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Dr. David F. Dinges

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The Trustees of the University of Pennsylvania
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14. ABSTRACT

The overarching objective of the AFOSR PRET Center for Countermeasures to Jet Lag and Sleep Deprivation was the completion and integration of basic scientific research from three university laboratories for the goal of developing technologies that overcome the performance-impairing problems and risks posed by jet lag and sleep deprivation. Major human research projects on the effects of induced jet lag and sleep deprivation and their mitigation by sustained low-dose caffeine and naps were undertaken at the University of Pennsylvania and Harvard, where investigators also performed work on development of a biomathematical model of the combined circadian and homeostatic regulation of performance and the effects of countermeasures (light, naps, caffeine). A parallel set of major research projects undertaken by investigators at Stanford University studied the effects of a range of wake-promoting substances in animal models. Additional ancillary objectives were also addressed at all sites. Center investigators also trained students and professionals in fatigue-countermeasure research; disseminated discoveries through hundreds of presentations and publications; and transitioned knowledge gained through Center research on countermeasures to the Air Force and related DoD, Federal and private environments.

15. SUBJECT TERMS

Jet Lag, Sleep Deprivation

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a. REPORT	b. ABSTRACT	c. THIS PAGE			David F. Dinges
Unclas	Unclas	Unclas		63	19b. TELEPHONE NUMBER (include area code) 215-898-9949

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AFOSR PRET Center on Countermeasures for Jet Lag and Sleep Deprivation

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Principal Investigator: David F. Dinges, Ph.D.
Professor of Psychology in Psychiatry
Chief, Division of Sleep and Chronobiology
Director, Unit for Experimental Psychiatry
University of Pennsylvania School of Medicine
1013 Blockley Hall
423 Guardian Drive
Philadelphia, PA 19104-6021
Phone: 215-898-9949
FAX: 215-573-6410
E-mail: dinges@mail.med.upenn.edu

Co-Principal Investigators: Charles A. Czeisler, Ph.D., M.D.
Professor of Medicine
Chief, Circadian, Neuroendocrine and Sleep Disorders Section
Division of Endocrinology
Department of Medicine
Brigham and Women's Hospital/Harvard Medical School
221 Longwood Avenue
Boston, MA 02115
Phone: 617-732-4013
FAX: 617-732-4015
E-mail: caczeisler@gcrc.bwh.harvard.edu

Dale M. Edgar, Ph.D.
Associate Professor
Director, Sleep and Circadian Neurobiology Laboratory
Sleep Research Center
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
701 Welch Road, Suite 2226
Palo Alto, CA 94304
Phone: 650-723-5876
FAX: 650-725-7341
E-mail: dmedgar@leland.stanford.edu

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2. OBJECTIVES

This AFOSR PRET Center on Countermeasures for Jet Lag and Sleep Deprivation had **three primary, overarching objectives**:

1. ***Completion of basic scientific research on the identification, development, validation and integration processes and technologies that could be used by the Air Force to overcome the performance-impairing problems and risks posed by of jet lag and sleep deprivation.*** Three university laboratories were actively involved in this primary objective: University of Pennsylvania School of Medicine (Dr. Dinges, P.I.); Brigham & Women's Hospital/Harvard Medical School (Dr. Czeisler, Co-P.I.); Stanford University School of Medicine (Dr. Edgar, Co-P.I.). The major human research projects undertaken at the University of Pennsylvania and Harvard sites were special experimental protocols designed to permit optimal double blind, placebo-controlled experiments of sustained, low-dose caffeine and its effects on human performance and alertness. Total and partial cumulative sleep deprivation protocols, and forced desynchrony protocols were performed at the two sites, respectively. Other investigators at Harvard (Drs. Jewett and Kronauer) performed work on development of a biomathematical model of the combined circadian and homeostatic regulation of performance, integrating the effects of countermeasures into the model (light, naps, caffeine) from the laboratories of Drs. Dinges and Czeisler. The third set of major research projects undertaken in the Center involved studies on the effects of a number of wake-promoting substances in animal models. Dr. Edgar and colleagues at the Stanford University School of Medicine completed these projects.

2. ***The dissemination, translation and transition of information on potential countermeasure technologies for jet lag and sleep deprivation to the broader scientific community, to the Air Force and related governmental agencies, and to industries that could ultimately use Center information to provide fatigue countermeasure technologies to the Air Force.***

3. ***The training of students and new scientists in the methods and approaches relevant to identifying novel ways of countering performance impairing fatigue during operations by Air Force personnel.***

Center investigators also pursued the following **20 ancillary objectives** related to the main goals of the Center. These efforts were often supplemented by support obtained by the P.I.s from other federal and private grants to Center investigators.

4a. Experiments on the effects of body posture and sensory restriction on performance and alertness in sleep-deprived individuals, to determine the potential of different environmental stimuli for enhancing performance (University of Pennsylvania site).
4b. Acquisition of new data on the magnitude of performance deficits upon awakening (i.e., Process W or sleep inertia) and its duration, for input into the biomathematical model of alertness (at the Harvard and University of Pennsylvania sites).
4c. Development of a database to establish the magnitude and predictors of inter-subject variability in neurobehavioral deficits from sleep loss and circadian disturbance (University of Pennsylvania site).
4d. Evaluation of different aspects of fatigue and acquisition of data on rest-activity cycles and fatigue in Air Force personnel engaged in night operations (University of Pennsylvania site).
4e. Obtain data on the effects of sleep deprivation on plasma cytokine levels in humans (University of Pennsylvania site).
4f. Perform study of the duration of sleep needed to recover from sleep deprivation (University of Pennsylvania site).

4g. Review, identification, and, when possible, development of the most promising ambulatory fatigue-detection technologies, to develop a miniaturized monitor that acquires and integrates data on an individual's alertness or performance capability while in the field (University of Pennsylvania site).

4h. Evaluation of the validity and reliability of miniaturized ambulatory technologies for tracking drowsiness during work involving sustained psychomotor vigilance (University of Pennsylvania site).

4i. Evaluation of EOG (eye movement) and EEG correlates of the homeostatic and circadian regulation of wakefulness and neurobehavioral functions in the 42.85 hour forced-desynchrony protocol, in an effort to identify on-line physiological markers of alertness (Harvard University site).

4j. Perform pre-clinical studies of the wake-promoting properties and compensatory sleep responses of Pemoline administration in rats, using the SCORE sleep-wake bioassay (Stanford University site).

4k. Conduct a clinical pilot study (6 subjects) investigating pemoline (Cylert®) as a countermeasure for excessive sleepiness and investigate the somnolytic action of this drug (Stanford University site).

4l. Perform pre-clinical studies on a non-nocturnal animal model (*Octadon degus)* for pharmacological comparison and validation of data obtained from a nocturnal species (rat) (Stanford University site). The development of a diurnal animal model could potentially speed the transition of new information on wake-promoting compounds from animals to humans.

4m. Conduct further evaluation of *Octadon degus* as a non-nocturnal animal model of sleep-wake regulation (Stanford University site). Because this species has strong crepuscular waking behavior, judiciously timed sleep deprivation allowed the assessment of compensatory sleep interaction with both the morning and evening episodes of SCN-dependent alerting compounds. Since humans also have two major episodes of physiological arousal across the circadian cycle, these data, and this animal model help expedite the transition of information on wake-promoting therapeutic efficacy and interaction with sleep loss, and make better pre-clinical predictions of how wake-promoting drugs will act in humans.

4n. Perform pre-clinical studies of two selective dopamine transporter blockers (GBR 12783 and 4'4"-difluro-3α(diphenylmethoxy)tropane, and one additional dopamine autoreceptor antagonist (UH-232) using the SCORE pre-clinical sleep-wake bioassay (Stanford University site). These experiments were designed to investigate the interaction of wake-promoting therapeutic pharmacology with the sleep homeostatic process. They helped clarify whether drug-binding affinity at the dopamine transporter site, or at the dopamine D2 autoreceptor site, directly correlates with efficacy and/or somnolytic drug actions. Such information will help us to make better initial predictions regarding the therapeutic potential of novel drugs (there are many uncharacterized novel compounds that are commercially available or can be made available from our industry associates), thus expediting our drug discovery transition efforts.

4o. Perform pre-clinical studies investigating the recovery sleep profiles of rapid eye movement (REM) sleep deprivation (Stanford University site). Chronic sleep restriction, recovery sleep after sleep deprivation, sleeping during the day (e.g., shift workers), and the use of many medications to manage diverse medical problems (e.g., sleep-wake disorders, blood pressure, depression) cause the displacement and/or inhibition of REM sleep. These studies were targeted at determining the physiological consequences of REM sleep loss or how it may influence the immediate or delayed component of compensatory sleep.

4p. Characterization of the photic phase response curve in the *Octodon degus* (Stanford University site). These experiments were designed to assess whether nocturnal and diurnal species employ different photic entrainment mechanisms, as suggested by Lee and colleagues in the literature. This is a critically important question with respect to the application of light treatment or the development of light-like pharmaceuticals for the treatment of jet-lag and sleep disorders in night-shift workers.

4q. Design of an engineering project to upgrade the SCORE-Sleep-Wake Bioassay technology for compatibility with modern operating systems and to provide numerous functional enhancements that will facilitate our Center's ongoing research efforts (Stanford University site).

4r. Investigation of the mechanism of action of modafinil (Stanford University site). These experiments determined if the dopamine transporter was necessary for modafinil's wake-promoting effects, and have proven to be informative toward the development of new lines of selective wake-promoting therapeutics.

4s. Clinical investigation of the effects of modafinil on alertness during sleep deprivation and night shift work (Harvard and University of Pennsylvania sites).

4t. Studies designed to characterized the effects of repeat acute and chronic wake-promoting therapeutic delivery (Stanford University site). These studies addressed critically important operational and safety questions regarding the chronic use of somnolytic wake-promoting drugs.

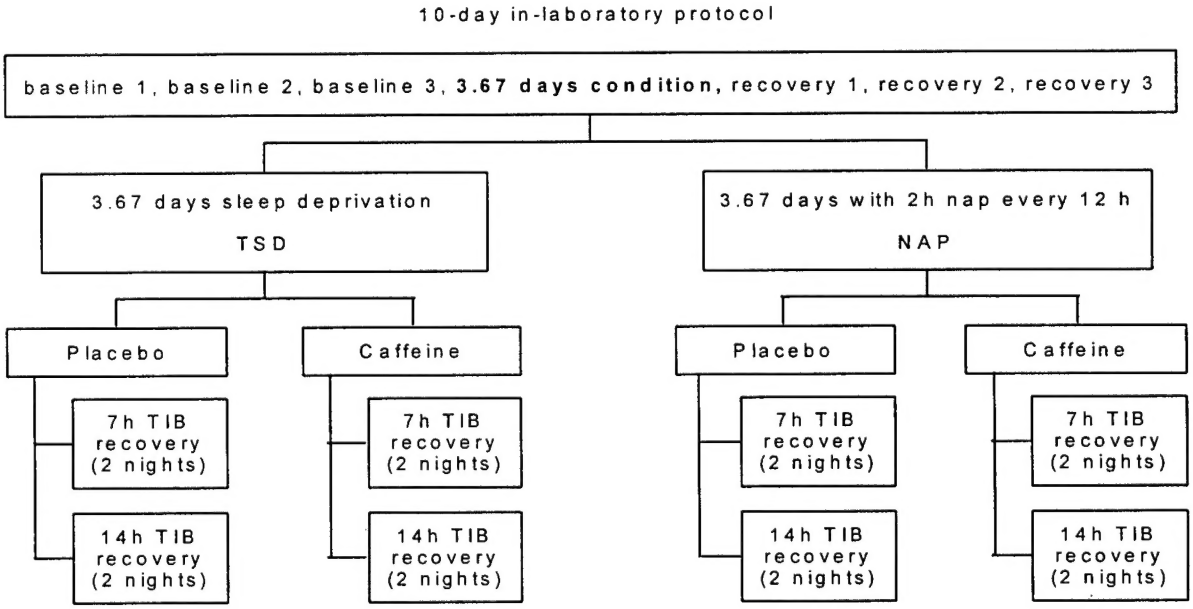
3. ACCOMPLISHMENTS / FINDINGS

Experiments were conducted at the three university sites simultaneously, under the direction of the P.I. at each site. The methods, accomplishments and findings from these studies are summarized below for each site individually. Greater detail regarding specific findings and additional experiments relevant to Center ancillary goals can be found in the 180 papers, chapters, abstracts, and technical reports generated by Center investigators during the period 1995-2000, listed after the accomplishments and findings.

A. University of Pennsylvania School of Medicine—Dr. David F. Dinges, Principal Investigator

The primary experimental study conducted at the University of Pennsylvania site involved a test of a novel use of naps and caffeine as separate and combined countermeasures to performance degradation during severe sleep deprivation. The laboratory experiment simulated sustained operations scenario in which healthy male subjects in the age range of Air Force personnel were required to perform quasi-continuously for 10 days while undergoing under intense physiological monitoring. The study design displayed in Figure 1 below was a double blind, placebo-controlled, randomized trial of sustained low-dose caffeine (0.3mg per kg, administered hourly) for 66 hours during 88 hours of sleep deprivation (i.e., TSD condition) versus 88 hours in which 2-hour nap opportunities were permitted every 12 hours (i.e., NAP condition). Thus the design permitted a direct test (1) of the effects of sustained low-dose caffeine as a wake-promoting countermeasure; (2) of the effects of naps as a fatigue countermeasure; and (3) of the interaction of sustained low-dose caffeine and naps. A 0.3mg/kg/hr caffeine dose was selected as a low dose because it is equivalent to giving a 175-lb (80kg) male 24mg caffeine hourly, resulting in a cumulative total of 578mg caffeine ingested in 24 hours, which is equivalent to 4-6 cups of coffee per day based on an estimated 100mg to 150mg caffeine per cup of coffee.

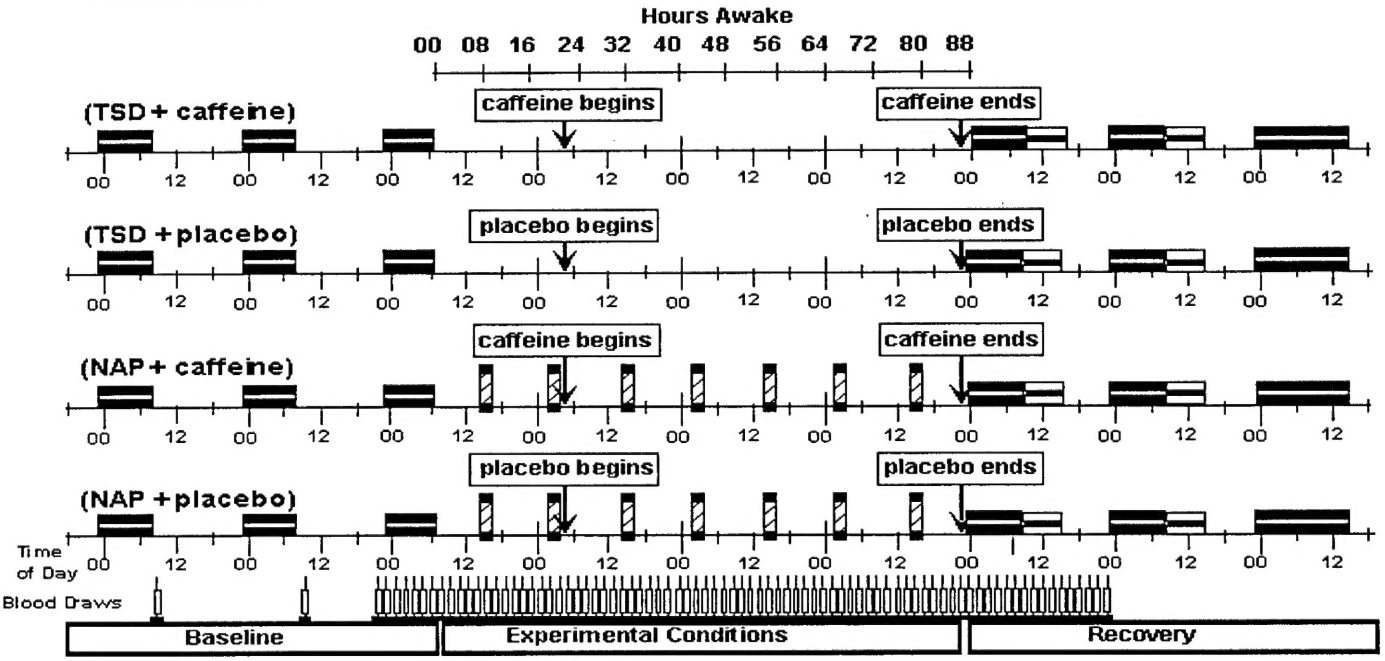
Figure 1. Schematic representing the overall study design



(1) Methods

A total of N = 58 male subjects (age range: 21 – 47 years) participated in this randomized, double-blind protocol (N = 617 were initially screened for the study). Following a 7 - 14 day period at home during which time subjects were monitored (actigraphy, sleep diaries, time stamped telephone logs) to ensure stable sleep/wake cycles, subjects completed a 10-day in-laboratory protocol. The protocol consisted of 3 baseline days/ nights, followed by 3.67 days (88 hours) of sustained wakefulness (with and without 2 x two-hour naps), and three recovery sleep nights. During the time in the laboratory, subjects' sleep and waking physiology (EEG, EOG, ECG, EMG, core body temperature), neurobehavioral functions (comprehensive performance assessments), endocrine functions (melatonin, cortisol, norepinephrine, cytokines), and plasma caffeine levels were monitored. Caffeine pill (0.3 mg per kg per hour) or placebo pill was begun after 22 hours into the 88-hour period, at 0530 hour on second day in the 88-hr period. Figure 2 displays the protocol sequence for the four conditions (n = 15 TSD + caffeine; n = 13 TSD + placebo; n = 15 NAP + caffeine; n = 15 NAP + placebo).

Figure 2. Schematic representing the 10-day in-laboratory protocol conducted at the University of Pennsylvania site, comparing four treatment conditions (TSD + caffeine; TSD + placebo; NAP + caffeine; NAP + placebo). Neurobehavioral test batteries were completed every 2 hours throughout all waking periods. EEG, ECG, EOG, and core body temperature were continuously recorded. Blood draws were taken via an indwelling catheter every 90 minutes from the last baseline night through the first recovery day. Baseline and recovery sleep periods are shown as horizontal bars; 2-hour nap periods during the 88-hour period are shown as vertical bars.



(2) Results – Pharmacology: Plasma caffeine levels

Plasma caffeine levels achieved with the 0.3mg/kg/hr dose regime in the TSD and NAP conditions are shown in Figure 3. In the caffeine groups a steady increase in plasma caffeine levels commenced from within 3.25 hours of the first administration (at 0530hr, which was 22 hours into the 88 hours), and continued increasing until reaching a plateau after approximately 29 hours. In the nap group, subjects received 5 fewer caffeine doses, since they were not awakened from their 2-hour naps for either caffeine or placebo pill administration. Therefore, during these nap periods the plasma caffeine curve shows a small decrease in the NAP subjects relative to the caffeine levels in the TSD subjects (i.e., open triangles in Figure 3 show the nap period dips in plasma levels as a result of no pill being administered to the NAP group during each nap). Table 1

summarizes the pharmacokinetics for both TSD and NAP conditions. Consistent with the dosing regime differences, the TSD condition resulted in a significantly higher maximum concentration, which tended to peak sooner (i.e., time taken to reach maximum concentration). However there was no difference between the TSD + caffeine and NAP + caffeine conditions in overall caffeine concentration as measured by area under the curve (AUC).

Figure 3. Average plasma caffeine levels for TSD and NAP conditions.

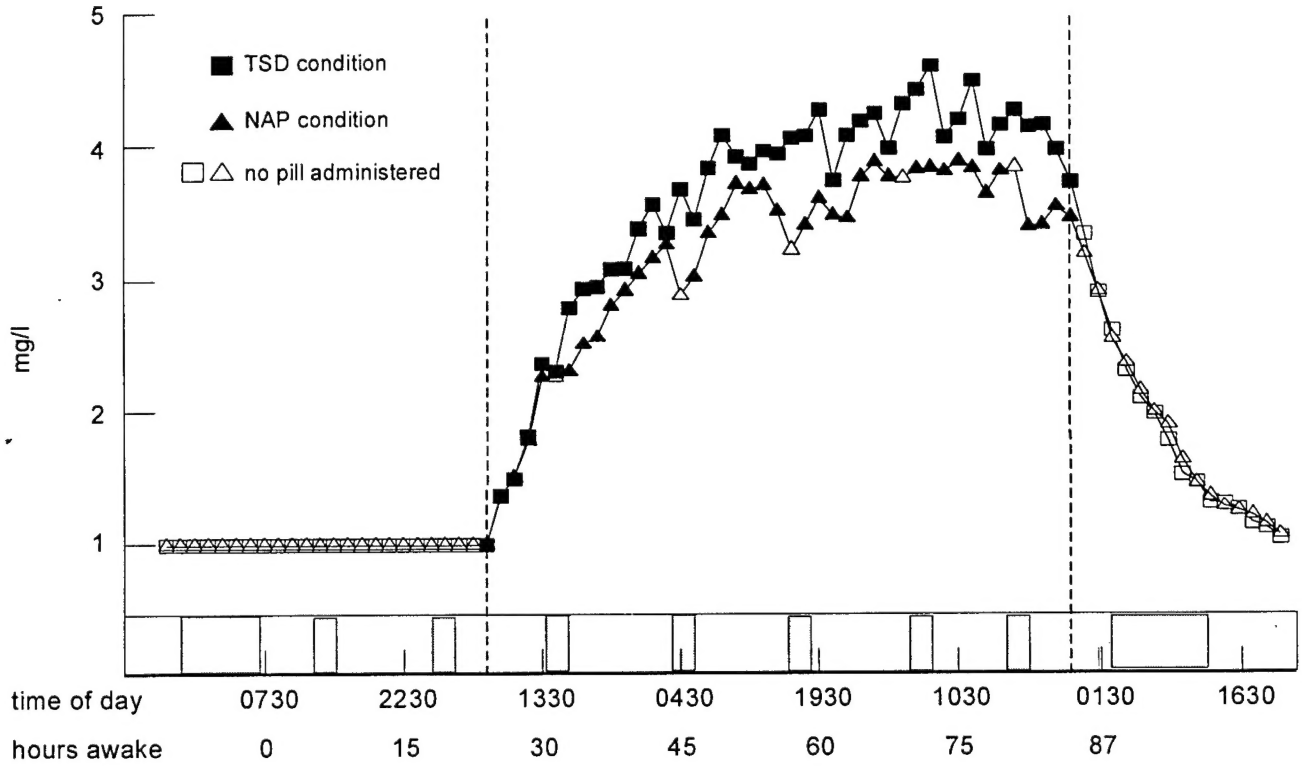


Table 1. Caffeine pharmacokinetics for the TSD + caffeine condition and NAP + caffeine condition.

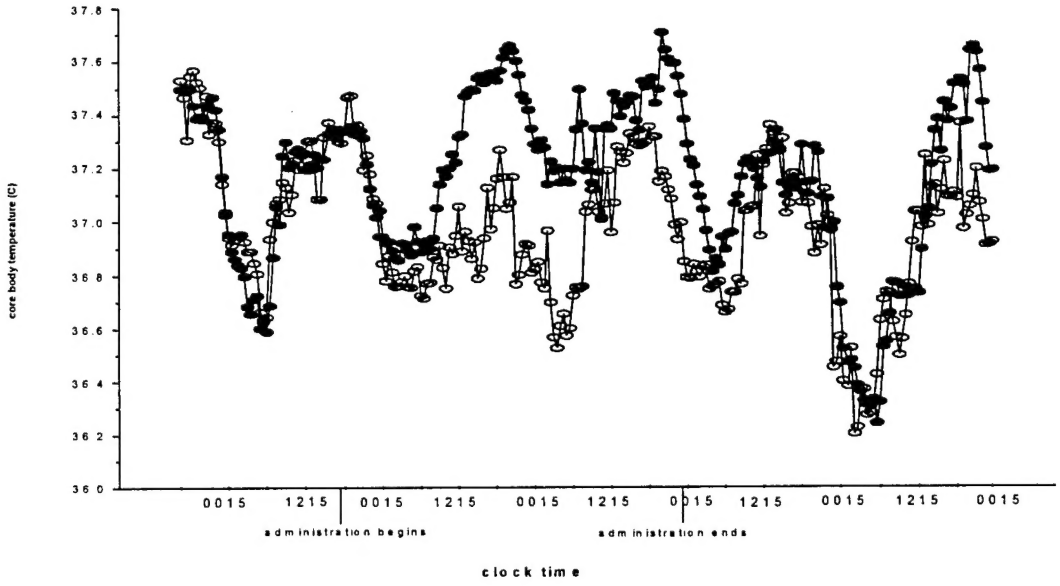
	TSD condition	NAP condition	difference between conditions
Maximum concentration (cmax)	5.9 ± 0.6 mg/l	4.4 ± 0.5 mg/l	p = 0.043
Time to maximum concentration (tmax)	50.9 ± 3.3 hr	43.64 ± 3.0 hr	p = 0.674
Area under the curve (AUC)	3.2 ± 0.3 mg/l	2.9 ± 0.3 mg/l	p = 0.531

(3) Results – Caffeine and core body temperature

To assess the effects of caffeine on core body temperature (CBT), rectal temperature recordings were continuous recorded throughout the 10-day laboratory protocol, using a flexible probe. CBT results from the TSD condition are shown in Figure 4, comparing average CBT curves for caffeine subjects versus placebo subjects. As expected, circadian variation is evident in both groups across the 5-day period of recording, including during the 88-hour period of continuous waking, during which caffeinepr placebo pills were

administered hourly. In the TSD + caffeine group (closed circles) a significant elevation ($p<0.001$) in core body temperature is evident relative to the TSD + placebo group (open circles), coincident with the steady increase in plasma caffeine levels. The magnitude of the temperature elevation was greatest during the first few hours of caffeine administration (mean difference between caffeine and placebo conditions = 0.51 ± 0.02°C). This hyperthermic effect of caffeine endured for approximately 18 hours following the first caffeine administration. The increase in CBT brought on by sustained low-dose caffeine intake appears to reflect a change in the mean temperature levels rather than a change in the circadian amplitude. We are currently analyzing data from the NAP + caffeine vs. NAP + placebo conditions to determine if this apparent thermogenic effect of caffeine is present when naps are permitted. We are also investigating a potential causal relationship between enhanced performance capabilities and elevated core body temperature levels in the caffeine group relative to the placebo group.

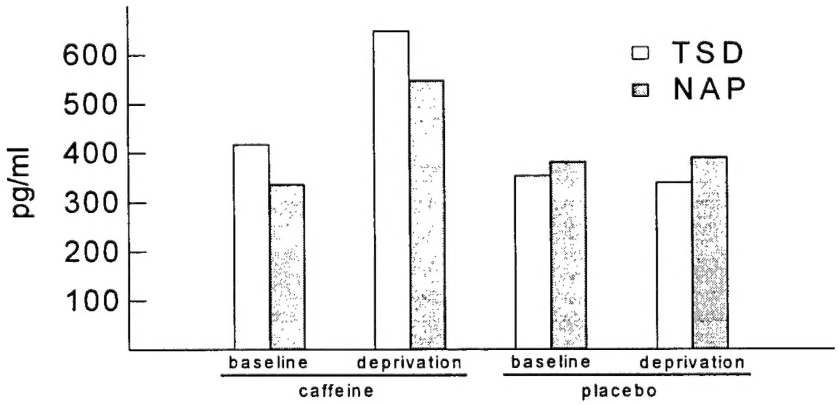
Figure 4. Core body temperature from TSD + caffeine (closed circles) and TSD + placebo (open circles) conditions.



(4) Results – Caffeine, sleep deprivation and norepinepherine

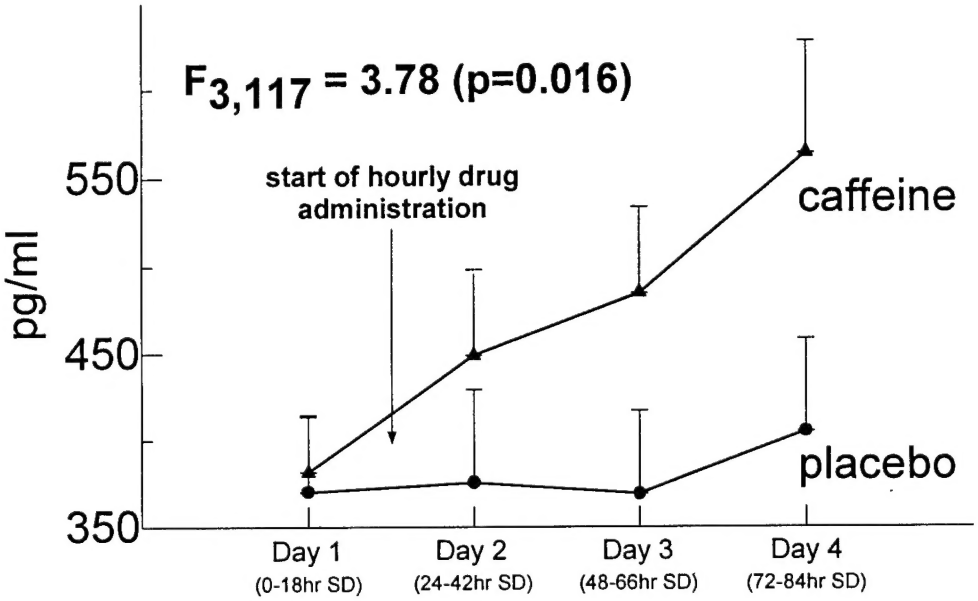
Plasma norepinepherine (NE) levels increased significantly across all four experimental conditions during the 88hr period ($p = 0.0001$), but the effect was more evident in the caffeine conditions (interaction $p = 0.057$). Figure 5 shows this effect. The result was further confirmed by ANOVA within each condition ($Fs < 1$ for both TSD + placebo and PSD + placebo conditions; $p = 0.026$, for TSD + caffeine; $p = 0.029$ for PSD + caffeine). Given that the effects of caffeine were much larger than those of placebo (with no difference in

Figure 5. Mean plasma norepinepherine levels for all conditions on baseline days and during the 88-hour period of total or partial sleep deprivation (i.e., naps).



plasma NE levels between TSD and PSD), subjects were pooled into two groups: those that received caffeine and those that received placebo. The 88-hr period was separated into four intervals: day 1 from 0730-0130hr (i.e., 0-18 hr); day 2 from 0730-0130hr (i.e., 24-42 hr); day 3 from 0730-0130hr (i.e., 48-66 hr); and day 4 from 0730-1930hr (i.e., 72-84 hr). A mixed-model ANOVA revealed the increases in plasma norepinephrine levels across days in the caffeine condition relative to the placebo condition ($p=0.016$). Figure 6 displays these results. We are currently investigating potential relationships between this increase in NE levels and other physiological (i.e., thermoregulatory, sleep) and endocrine (i.e., cortisol, melatonin, thyroid hormones) effects of caffeine. It is noteworthy that preliminary evaluations to date suggest that the effects of caffeine on NE were not accompanied by cardiovascular sequelae. In fact, there was no evidence in performance on a tracking task that sustained low-dose caffeine produced psychomotor agitation. No subject had to be withdrawn from the protocol due to an adverse reaction to caffeine. Therefore, the NE results support a caffeine effect on circulating catecholamines, but apparently not at a level that resulted in cardiovascular or behavioral adverse events. Caffeine did, however, have other physiological and neurobehavioral effects.

Figure 6. Plasma norepinepherine levels for the caffeine and placebo conditions, pooled across TSD and NAP conditions.



(5) Results – Effect of caffeine on nap sleep structure

As expected, there were no significant differences in any nap sleep polysomnograhic (PSG) variables between naps 1 and 2, which occurred on the first afternoon and night, respectively, of the initial 24 hours in the 88-hr period, prior to either caffeine administration or sleep deprivation. The effects of hourly caffeine vs. placebo administration on nap sleep physiology was assessed by comparing nap PSG data from the NAP + caffeine condition to results from the NAP + placebo condition. Across naps 3 through 7, which occurred sequentially every 12 hours from the 34 hour to the 82 hour of the 88-hr period, as the amount of partial sleep deprivation progressed, naps had increased total sleep time (TST) (Figure 7), increased slow wave sleep (SWS) (Figure 8), and decreased wake after sleep onset (WASO) (Figure 9)] (all ps < 0.005). Relative to placebo, caffeine reduced nap total sleep time (Figure 7) by an average of 13 minutes ($p < 0.001$), primarily by increasing sleep latency (Figure 10) an average of 10 minutes ($p < 0.001$), but it also tended to reduce time in slow wave sleep (Figure 8), especially in naps 3 ($p = 0.08$) and 4 ($p = 0.03$), and reduce REM sleep minutes ($p = 0.02$). Only the amount of SWS (Figure 8) showed a condition by time interaction ($p = 0.043$), being reduced in nap 3 by an average of 8.4min ($p = 0.081$) and in nap 4 by 12.2min ($p = 0.036$). These SWS deficits were associated

with the rising slope of the plasma caffeine pharmacokinetic curve. The effects of sustained low-dose caffeine on nap sleep are currently being evaluated relative to the effects of caffeine and naps on performance, mood, and endocrine responses throughout the experimental protocol. Figure 11 illustrates the mean percentages of sleep stages for naps 3 to 7, and reveals that with caffeine sustained in plasma, sleep during the 2-hr nap sleep opportunities was (on average) less efficient by approximately 10% and included proportionally more stage 1 (light) sleep. These data suggest that caffeine did not prevent nap sleep, but it did reduce its quantity and quality. Quantitative EEG power spectral analyses of nap sleep are underway to establish the effects of caffeine on slow wave activity, the putative homeostatic marker of sleep drive.

Figure 7. Total sleep time in 2-hr nap opportunities every 12 hours across an 88-hr period. Caffeine vs. placebo conditions.

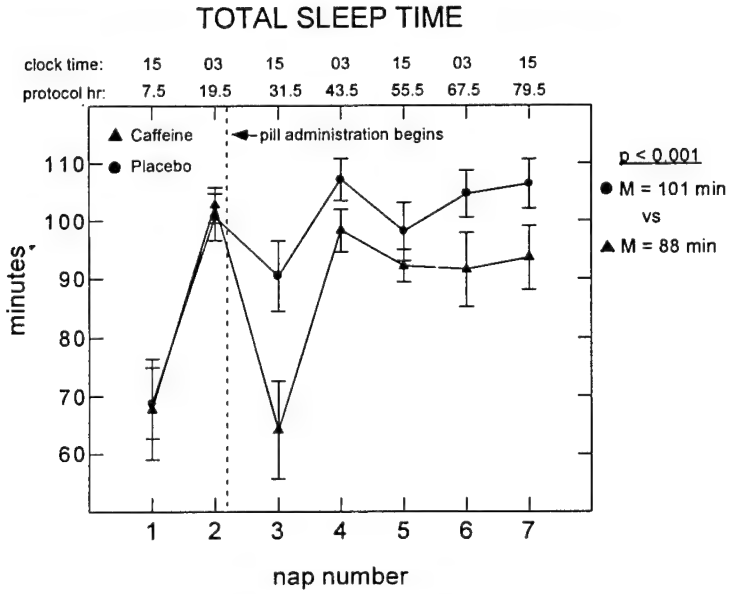


Figure 8. Slow wave sleep in 2-hr nap opportunities every 12 hours across an 88-hr period. Caffeine vs. placebo conditions.

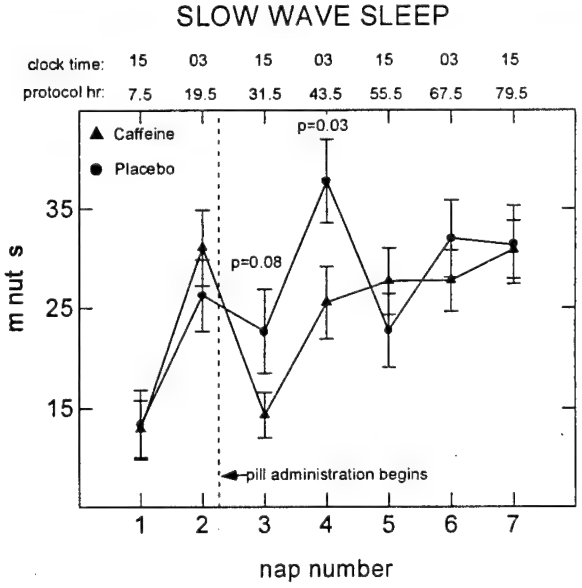


Figure 9. Total sleep time in 2-hr nap opportunities every 12 hours across an 88-hr period. Caffeine vs. placebo conditions.

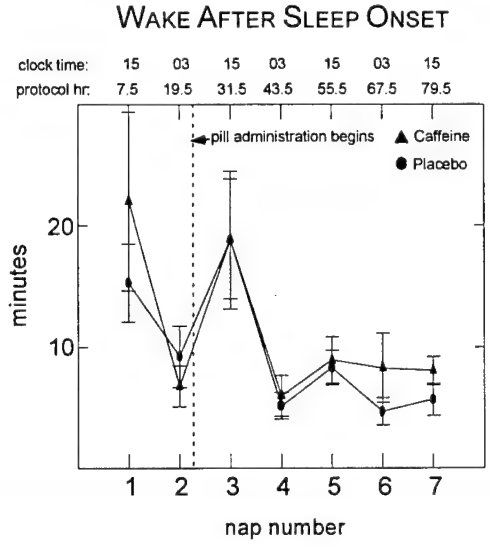


Figure 10. Slow wave sleep in 2-hr nap opportunities every 12 hours across an 88-hr period. Caffeine vs. placebo conditions.

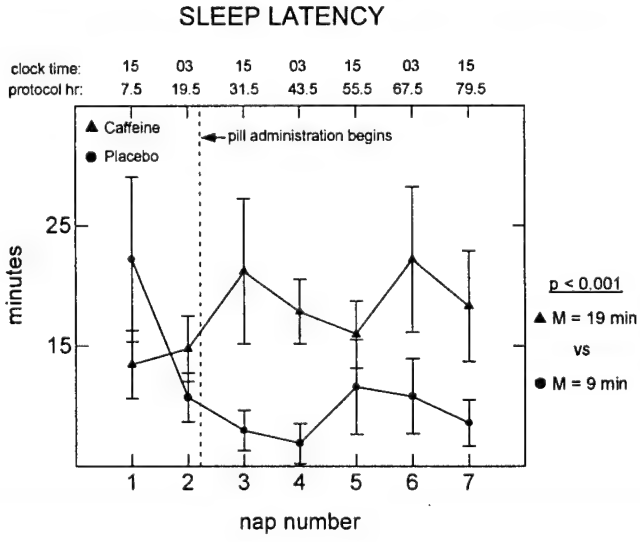
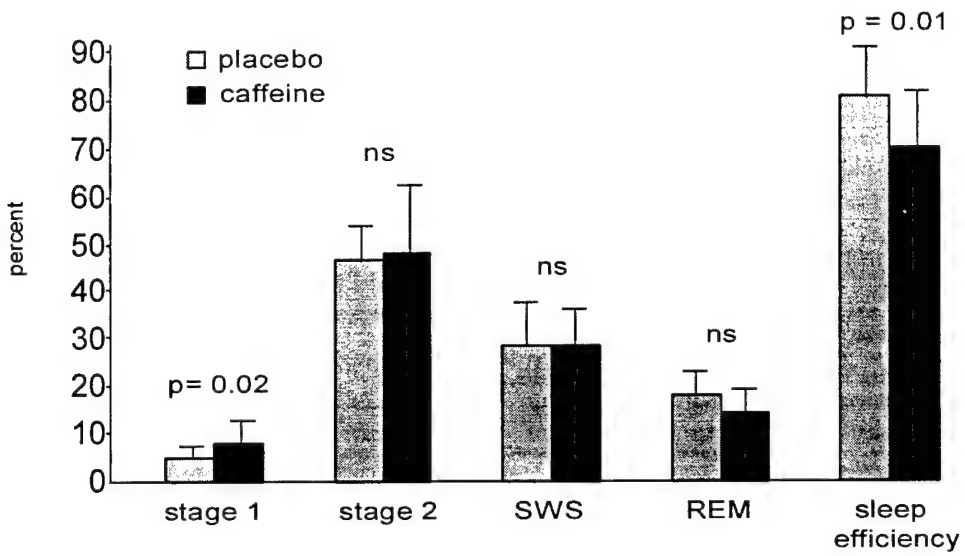


Figure 11. Mean sleep stage percentages for naps 3 to 7, for caffeine vs. placebo condition.



(6) Results – Effect of caffeine and sleep deprivation on neurobehavioral functioning

The 88-hr period of total sleep deprivation markedly deteriorated virtually every behavioral and physiological marker of performance, alertness, and mood. Analyses are still underway on the large number of outcome variables, but the results thus far have been quite consistent in showing that in terms of behavioral efficiency, the conditions ranked from best to worst were as follows: NAP + caffeine, NAP + placebo, TSD + caffeine, TSD + placebo condition (see Table 2 and Figures 12, 13, 14, 15, 16). The most serious performance failure involves falling asleep (sleep attacks = SA) at computer console. Table 2 clearly reveals the fact that SA data for the 54 subjects thus far analyzed shows the clear advantage NAP conditions had over TSD conditions in preventing sleep attacks.

Table 2. Summary of PVT trials resulting in sleep attacks (SA) while performing.

Experimental condition	n	subjects who had >1 SA	% of subjects who had >1 SA	# of perform. trials with >1 SA	total number of SAs	time within 88-hr period for 1st SA (hr)	time of day for 1st SA
TSD + placebo	14	8	57%	29	173	23	06:00
TSD + caffeine	12	5	42%	16	59	23	06:00
NAP + placebo	13	2	15%	3	3	72	08:00
NAP + caffeine	15	2	13%	2	3	50	10:00

Analyses completed on the performance assay most sensitive to sleep loss and jet lag (i.e., lapses on the psychomotor vigilance task [PVT], which was invented in our laboratory) indicate that sustained low-dose caffeine reduced the frequency of lapses for up to 22 hr of administration (i.e., through the entire second day of TSD, thereby extending behavioral efficiency for up to 44 hr of TSD) relative to the placebo control condition ($p = 0.02$). Figures 12, 13 and 14 display the PVT results. Caffeine also tended to improve the fastest reaction times ($p = 0.06$) as shown in Figure 13. However, it had no effect on cognitive throughput tasks such as digit symbol substitution performance (Figure 15), or on short term memory performance (Figure 16), both of which

tended to occur in the latter portion of each performance test bout. Most remarkable was the complete absence of a main effect or interaction over time from caffeine on any of the subjective scales used to measure sleepiness (Figures 17 and 18), fatigue (POMS), alertness (VAS), or effort required to remain awake. All of these subjective dimensions only showed significant main effects (i..e., deterioration) over the 88 hr TSD period ($p < 0.00001$). Although remarkable, the failure to find statistically significant effects of sustained low dose caffeine intake for 66 hours on all subjective measures was consistent with the fact that when asked to indicate what drug they thought they had receive each hour of the trial, subjects were completed unable to reliably detect (i.e., better than chance) whether they were receiving caffeine or placebo! This suggests that the effects of caffeine on performance were not due to placebo effects or demand characteristics, but rather, reflected genuine caffeine-induced performance enhancements in psychomotor vigilance.

Although sustained plasma levels of caffeine after a night without sleep tended to improve performance for at least 22 hours, the alertness-promoting effects of caffeine were small in comparison to the repeated nap countermeasure. Permitting subjects to sleep for up to 2 hours every 12 hours (i.e., for no more than 3.7 hours per day for 4 consecutive days, markedly improved all performance outcomes relative to total sleep deprivation

across the 88 hours (Figures 12–16)—in many cases holding performance near baseline levels. However, like caffeine, the effects of naps were not detectable in subjective ratings of sleepiness/alertness (Figures 17-18).

Figures 12 through 18: Open squares = TSD + placebo condition. Open triangles = TSD + caffeine condition. Closed diamonds = NAP + placebo condition. Closed circles = the NAP + caffeine condition. In all Figures, hourly administration of caffeine or placebo pills began at 22 hours time awake and ended at 86 hours.

Figure 12. PVT performance lapses (lower values = better performance).

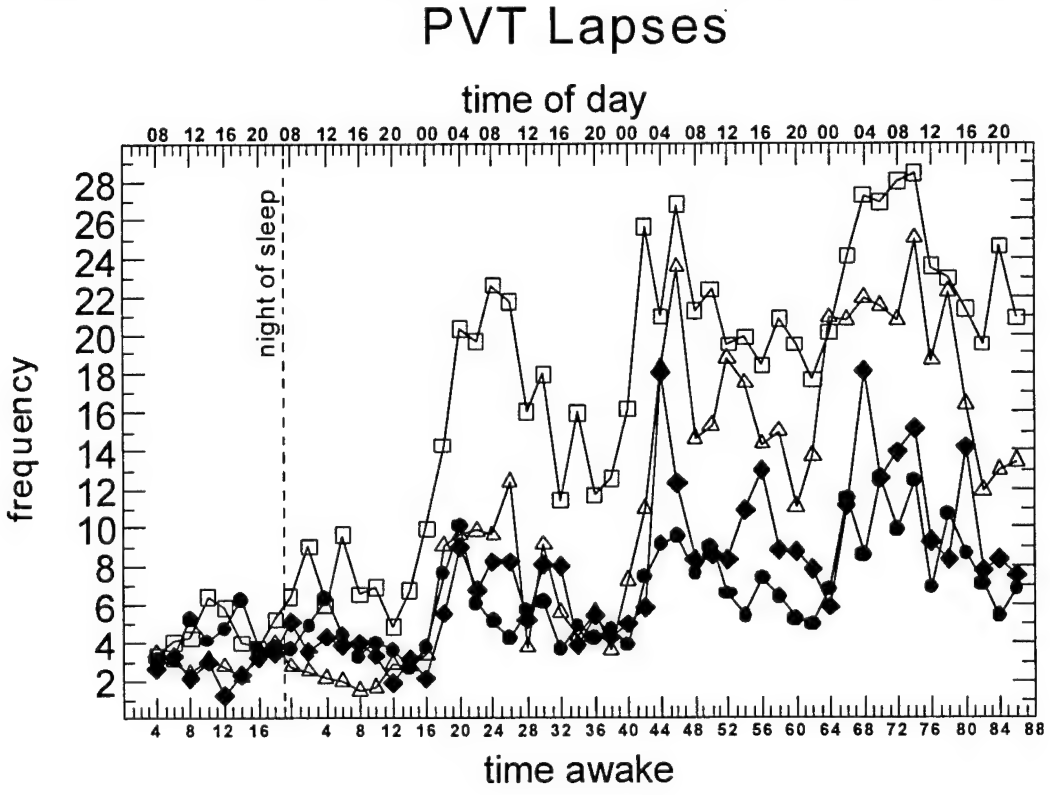


Figure 13. PVT fastest RTs performance (lower values = better performance).

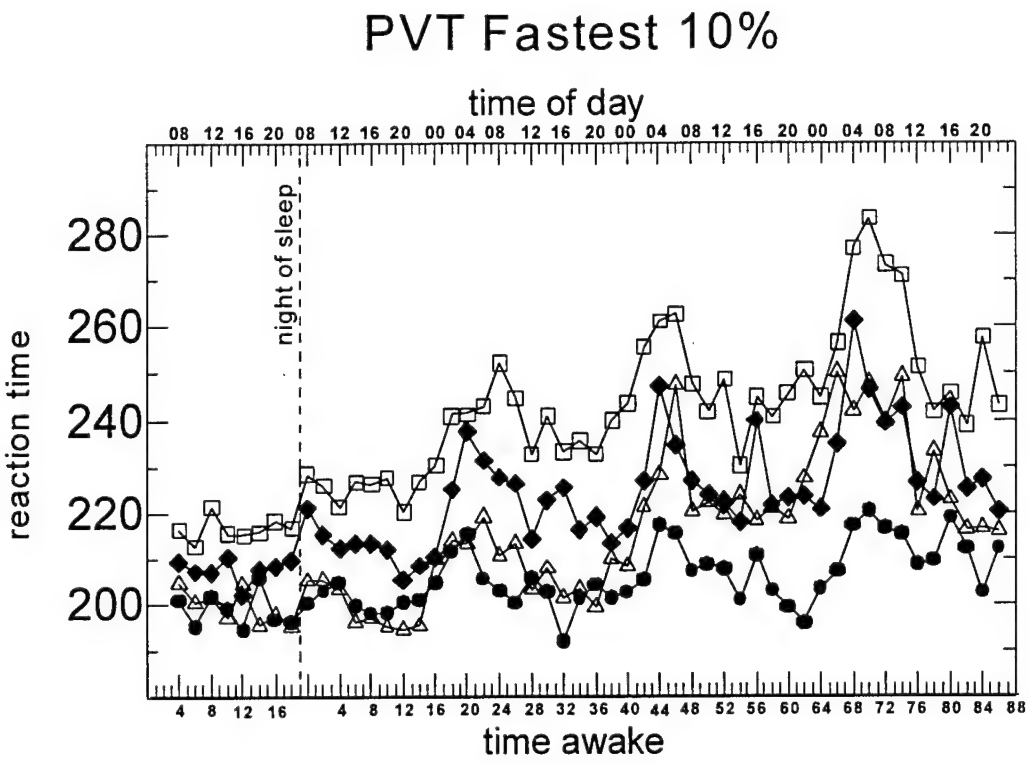


Figure 14. PVT slowest 10% (1/RT) performance (higher values = better performance).

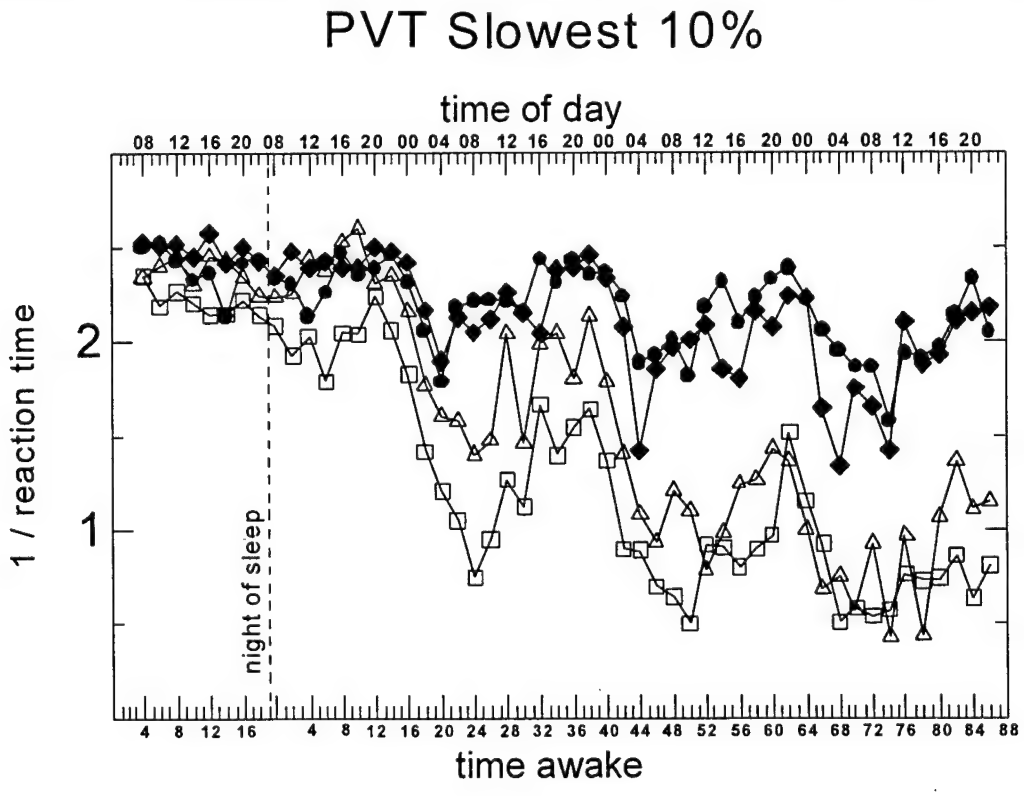


Figure 15. Digit symbol substitution task (DSST) performance (higher values = better performance).

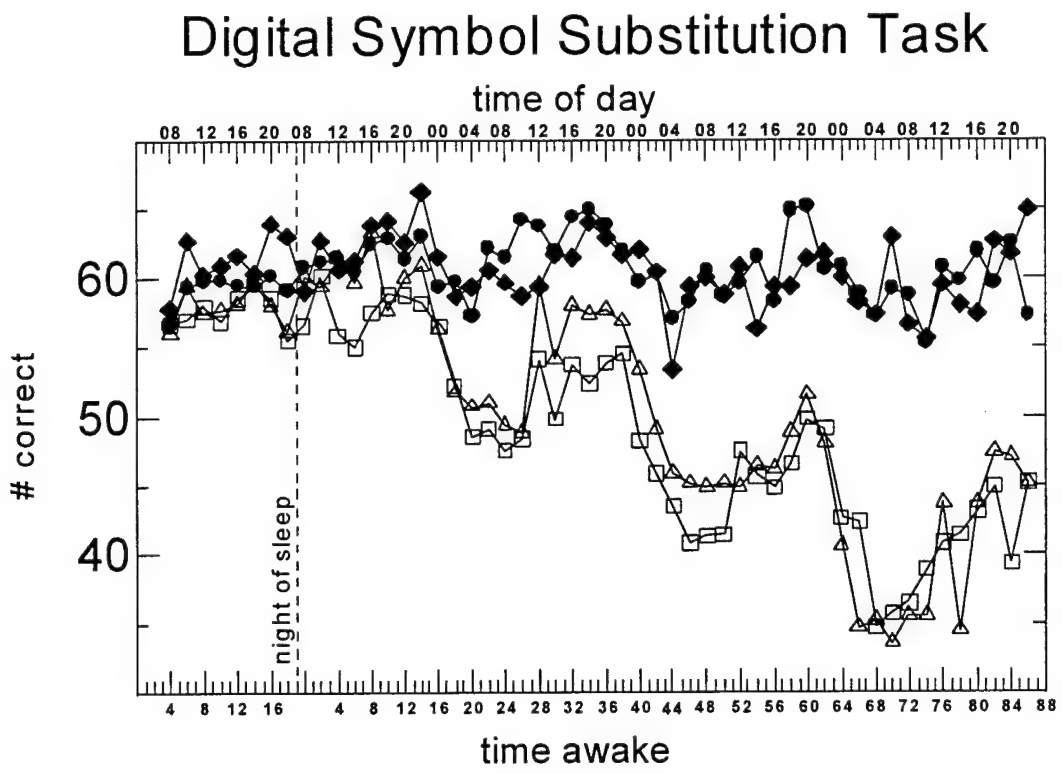


Figure 16. Probed recall memory task (PRM) performance (higher values = better performance).

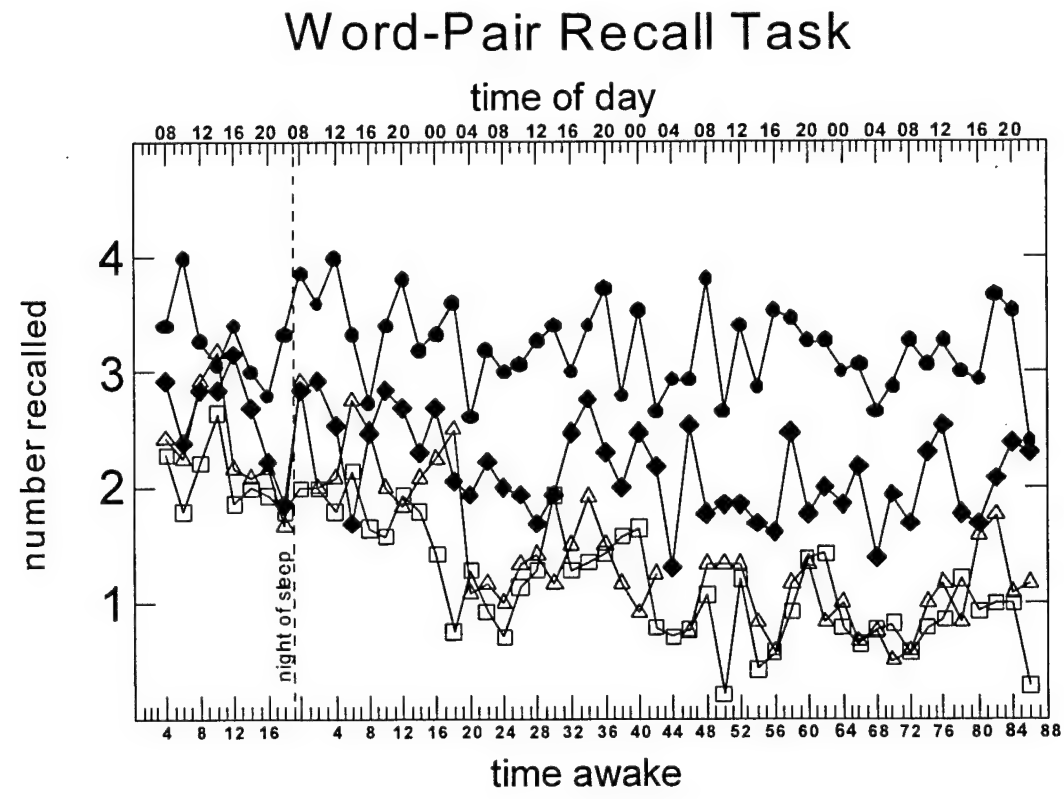


Figure 17. Stanford Sleepiness Scale (SSS) ratings (higher values = sleepier).

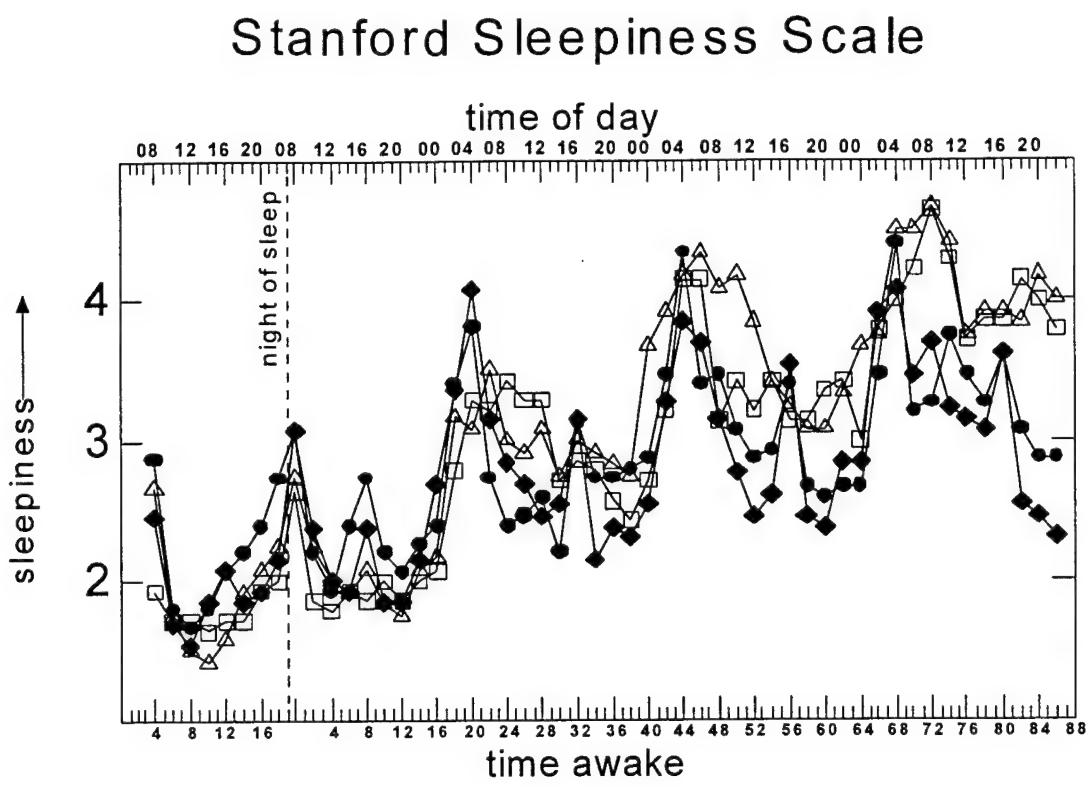
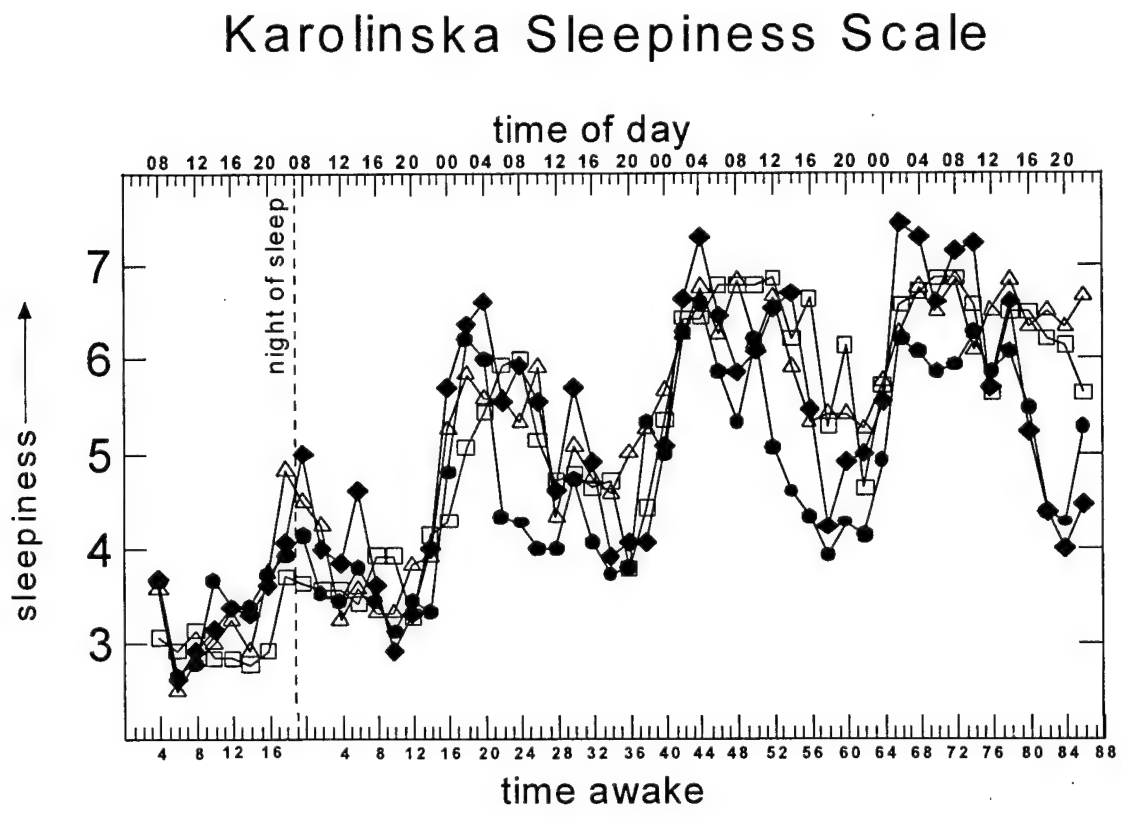


Figure 18. Karolinska Sleepiness Scale (KSS) ratings (higher values = sleepier).



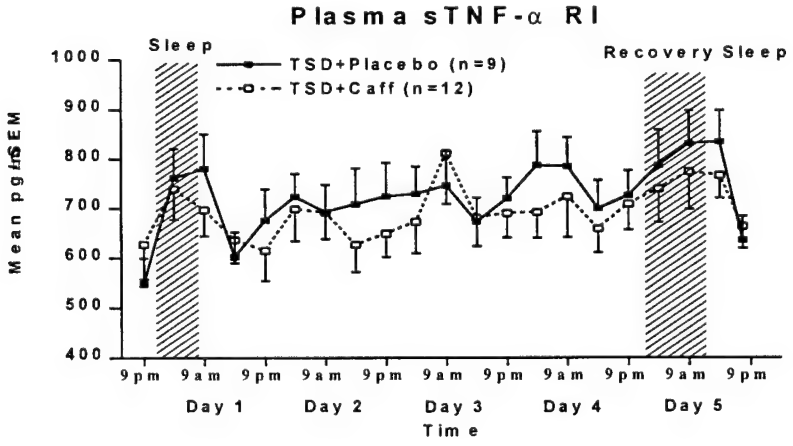
(7) Results – Effect of caffeine on sleep inertia.

Sleep inertia refers to the period of impaired performance upon awakening from sleep. It can be especially severe and prolonged when the awakening is abrupt and the sleep follows a period of total or partial sleep deprivation. Analyses were performed to determine whether sustained low dose caffeine had an effect on sleep inertia (as evident in PVT and cognitive performances) in the NAP conditions. Sleep inertia was evident in PVT performance, but not in cognitive performance, probably owing to the latter occurring later in the test bout. As expected, a significant main effect for days of sleep restriction was found ($p = 0.001$), revealing that PVT performance lapses increased over days of extended wakefulness in the NAP conditions irrespective of caffeine/placebo condition. Furthermore, a significant main effect of circadian phase was observed ($p < 0.001$), as performance lapses occurred more often during the night than during the day regardless of drug condition. Finally, there was a significant interaction of performance test bout by drug condition ($p = 0.002$). Performance lapses in the NAP + placebo condition showed dramatic sleep inertia effects in the test bout immediately following each nap. However, this impairment was not evident in the post-nap sleep inertia tests bouts of the NAP + caffeine condition. In fact, there were twice as many performance lapses in the test bout immediately after each nap relative to all other test bouts ($p < 0.001$). Consequently, an unexpected benefit of sustained low-dose caffeine was the elimination of the only negative performance consequence of naps (i.e., sleep inertia). This helps explain why the NAP + caffeine condition yielded the best performance of all conditions, despite the reduction in sleep efficiency produced by caffeine (see Figures 7-10). The caffeine elimination of sleep inertia lapsing can be seen in Figure 12, in that the NAP + caffeine condition does not show the periodic (12-hr) spikes in lapsing seen in the NAP + placebo condition. This is a new discovery, which suggests that sleep inertia can be blocked pharmacologically, and that the mechanism may be mediation by adenosine receptors. We have submitted a manuscript detailing this novel finding for rapid publication in a major scientific journal.

(8) Results – Sleep deprivation and immune function

In order to identify the effects of sleep deprivation, nap and caffeine countermeasures on human immune function, blood gathered every 6 hr in the protocol was analyzed by enzyme-linked immunoassays for selected cytokines and their soluble receptors including sTNF-αRI, sTNF-αRII, IL-6, sIL-2R, IL-10, and TNF-α. Caffeine had no differential effects on plasma levels of these cytokines or their receptors. However, interactions between the effects of time in 88-hr period and sleep deprivation level (TSD vs. NAP) were detected for sTNF-αRI and IL-6, but not for sTNF-αRII, sIL-2R, IL-10, and TNF-α. Figure 19 shows the TSD results for sTNF-αRI. Relative to the NAP condition, subjects in the TSD condition had elevated plasma levels of sTNF-αRI on day 2 ($p = 0.04$), day 3 ($p = 0.01$) of the 88-hr period, and across days 2-4 of total and partial sleep loss ($p = 0.01$), and elevated levels of IL-6 on the final day of the 88-hr period ($p = 0.04$). These changes appeared to reflect elevations of the homeostatic drive for sleep, since they occurred in TSD but not the NAP conditions, suggesting that naps may also serve as a countermeasure to inflammatory responses to sleep deprivation.

Figure 19. Plasma sTNF-αRI levels from TSD conditions.



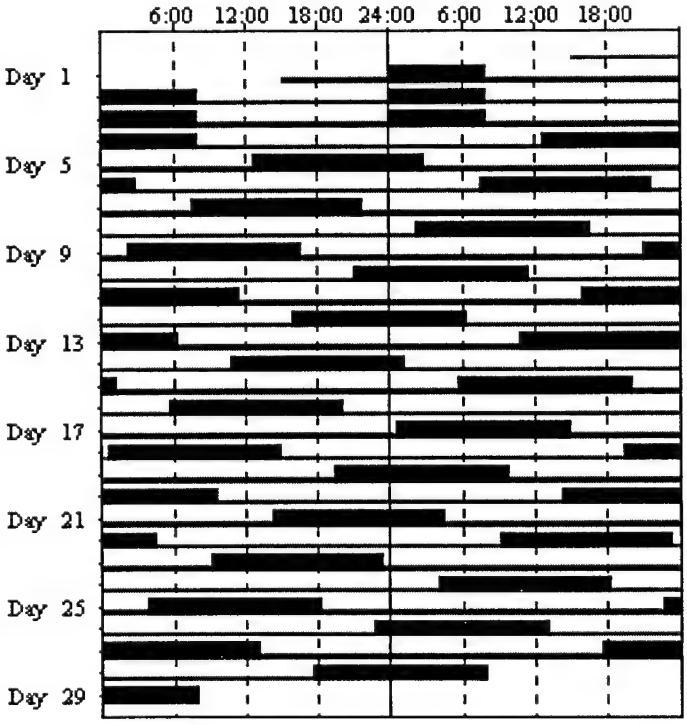
B. Brigham and Women's Hospital/Harvard Medical School—Dr. Charles A. Czeisler, P.I.

The primary experimental study conducted at the Brigham and Women's Hospital / Harvard Medical School site involved a new forced desynchrony protocol developed to address the specific aims and test the effects of caffeine on the endogenous circadian pacemaker and homeostatic drive for sleep. Prior to the beginning of the active grant period, we had investigated the interaction of sleep homeostasis and circadian rhythmicity in which the rest-activity cycle was scheduled to a 28-hr, 20-hr or 11-hr period. To investigate the interaction of sleep homeostasis and circadian rhythmicity in conditions in which wakefulness is extended to durations such as occur during Air Force operations, we successfully implemented a new forced desynchrony protocol. In this 29-day protocol subjects were scheduled to a 42.85-hr cycle on which they are scheduled to be awake for 28.57hr (2/3 of 42.65hr) and scheduled to sleep for 14.28hr. This 42.85hr schedule was started after 3 baseline days. A total of N = 16 subjects successfully completed this protocol.

(1) Subject selection and study protocol.

Prior to the inpatient study, each prospective subject received an extensive medical and psychiatric screening. Subjects who responded to advertisements in the community were given a brief telephone screening to determine initial suitability and interest. Next came a medical history and physical examination from a physician, a standard panel of blood and urine chemistries, a 12-lead EKG, and a urine toxicological analysis. Subjects also had to score within the normal range on a series of standard psychological and sleep questionnaires, to rule out self-reported psychiatric or sleep disorders. Next they met with a clinical psychologist or psychiatrist to rule out personal or first-order relative history of past or present major psychopathology. Finally, subjects were interviewed by an Investigator to determine suitability for the protocol and given a complete informed consent briefing, concluding with obtaining full written informed consent. Subjects successfully completing all stages of the screening process were required to maintain a regular sleep/wake schedule for at least two weeks prior to participating, and were asked to refrain from intake of any caffeine, nicotine, alcohol, prescription or over-the-counter medications, health food supplements, or illicit substances. Compliance with the sleep/wake schedule was verified by requiring the subjects to telephone a time-stamped voicemail system prior to going to bed and after waking up, and through estimations of sleep and wake from wrist actigraphic monitoring. Drug-free status was verified with a second urine toxicological analysis upon admission to the study unit.

A total of 16 healthy, young men (ages 18-30 years) were studied in this 29-day, inpatient research protocol (see Figure at right). Following an initial baseline assessment interval consisting of 3 days of 8-hr sleep episodes and 16-hr wake episodes scheduled to occur on their habitual, pre-study schedule, subjects were placed on a "forced desynchrony protocol." Enforced wakefulness was maintained for 28.57 hr and subjects were required to remain in bed for 14.28 hr. This "42.85-hr day" (versus the standard "24-hr day) was repeated for 14 cycles. Thus, with the sleep/wake schedule outside the range of entrainment of the intrinsic circadian timing system, with light exposure during scheduled wake episodes being maintained at levels low enough (< 15 lux) to have a minimal circadian phase shifting or entraining effect, and with subjects maintained in an environment free of obvious



information about time, the circadian timing system of each subject "free ran" at the intrinsic period, which averages 24.18 hr.

This protocol allowed for simulations of multiple conditions relevant to Air Force operations: extended hours of enforced wakefulness (28.54 hr), night operations (a portion of each wake episode occurred during the range of circadian phases of the subjective night), and jet lag (each sleep and wake episode was initiated at a different circadian phase).

The ingestion of low-dose, repeated administration caffeine capsules was tested as a countermeasure to the deficits in neurobehavioral functions observed during times of sleep loss with encountered across a full range of circadian phases. All subjects ingested placebo capsules hourly during scheduled wake episodes in the three baseline days. During forced desynchrony, half (n = 8) received only placebo capsules and half (n = 8) received a low dose of caffeine (0.3 mg/kg/hr). Again, each subject ingested a capsule each hour during scheduled wakefulness, and double-blind conditions were maintained throughout the study. It was initially thought that we might need to assess a higher dose of caffeine (0.6 mg/kg/hr) to significantly attenuate neurobehavioral deficits during extended wakefulness across a full range of circadian phases, but our initial mathematical modeling in combination with plasma assays for caffeine level in our first few subjects clearly indicated that a higher dose would exceed our desired maximal dose, risking possible side effects (e.g., diuresis, psychomotor agitation).

Intensive physiological monitoring was conducted on subjects throughout the protocol. Circadian phase, amplitude, and free-running period were determined from two measurements of oscillating biological processes regulated by the intrinsic circadian timing system – core body temperature and plasma melatonin. Subjects wore rectal temperature sensors throughout the experiment, which allowed for minute-by-minute recording of core body temperature. An indwelling, forearm intravenous catheter allowed collection of hourly blood samples for analysis of circulating melatonin levels, as well as determination of caffeine level of those subjects receiving caffeine capsules. Statistical procedures for estimating circadian phase, amplitude, and free-running period are described in Czeisler et al., 1999 (published in *Science*).

Comprehensive neurobehavioral assessment batteries were delivered via computerized system each 2-hr during scheduled wakefulness throughout the protocol. These 30-minute assessments were monitored by research staff to ensure subjects maintained wakefulness and continued to put forth reasonable effort. This battery was comparable to the one given at the University of Pennsylvania site, to allow for future data comparisons between the related protocols and comparable dependent variables for the biomathematical modeling. The assessments consisted of the following measures:

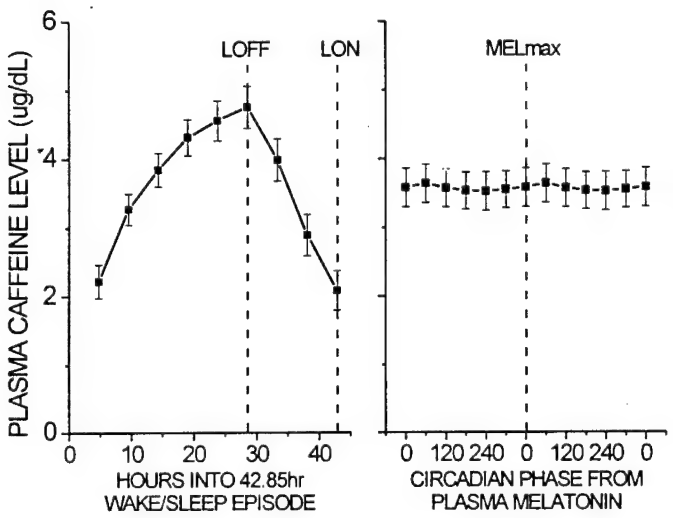
- Karolinska Sleepiness Scale (KSS): subjective sleepiness
- Psychomotor Vigilance Task (PVT): visual motor, simple reaction time and visual vigilance
- Probed Recall Memory task (PRM): cued-recall, short-term memory for visually-presented verbal material
- Addition Task (ADD): mental calculation and cognitive throughput
- Digit Symbol Substitution Task (DSST): number-to-symbol matching and cognitive throughput
- Nonlinear Tracking Task (TRACK): psychomotor steadiness and visual motor tracking
- Karolinska Drowsiness Test (KDT): electrophysiological measures (scalp EEG and eye-movement recording) under standardized, unstimulated, sedentary conditions
- Fitness and mood scales (MOOD): visual analog scales for self-reporting of physical and mental status
- Performance Evaluation and Effort Rating Scales (PEERS): self-report of amount of effort expended to achieve a certain level of estimated performance

Following data collection, each experimental neurobehavioral measurement was assigned values for duration of prior scheduled wakefulness and circadian phase. Thus, it was possible to separately average data points, first within subject and then across subjects within drug condition, by either circadian phase bin or by bin of prior scheduled wakefulness. This process allows for determination of the independent **sleep/wake**

homeostatic and **circadian** contributions to the modulation of waking neurobehavioral functioning. Similar procedures were carried out for analysis of the polysomnographic (sleep recording) data. In addition, this procedure allowed for determination of the **complex, nonlinear interaction** of the sleep/wake homeostatic system in its regulation of the amplitude of circadian system's modulation of waking neurobehavioral functioning and sleep structure, as described below for the results. Data were compared across subjects by drug condition with repeated measures analysis of variance (rANOVA). The Huynh-Feldt correction for sphericity was applied, but the original degrees of freedom are reported. Post hoc analyses utilized the T-test for least significant differences (T[LSD]). All analyses were conducted with SAS software (Version 6.12 for PC).

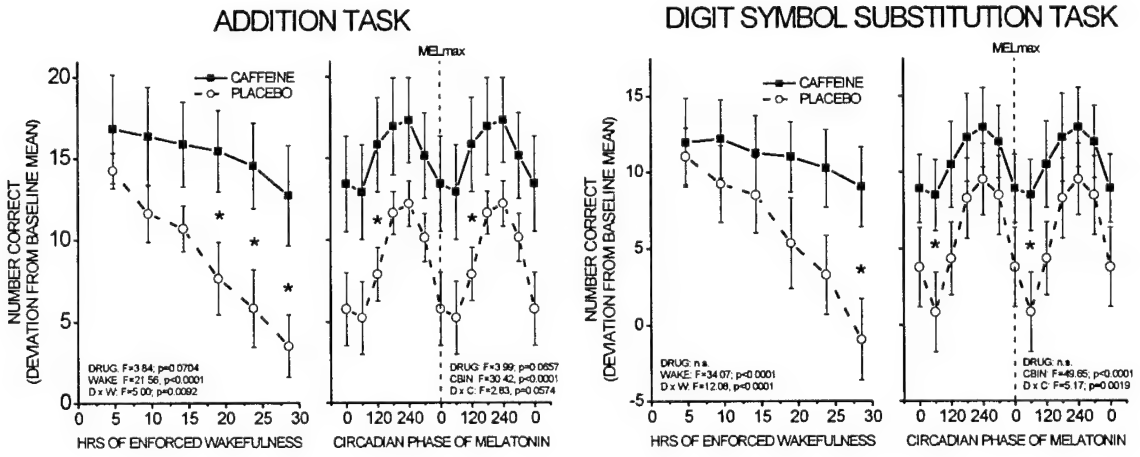
For the figures below, the left panels represents data averaged with respect to duration of prior wakefulness, to address the sleep homeostatic component of sleep and neurobehavioral regulation. The right panels represents data averaged with respect to the maximum level of endogenous melatonin, which corresponds approximately to the middle of the habitual nocturnal sleep episode, and illustrates the circadian modulation of sleep and neurobehavioral measures.

(2) Results – Caffeine plasma levels.



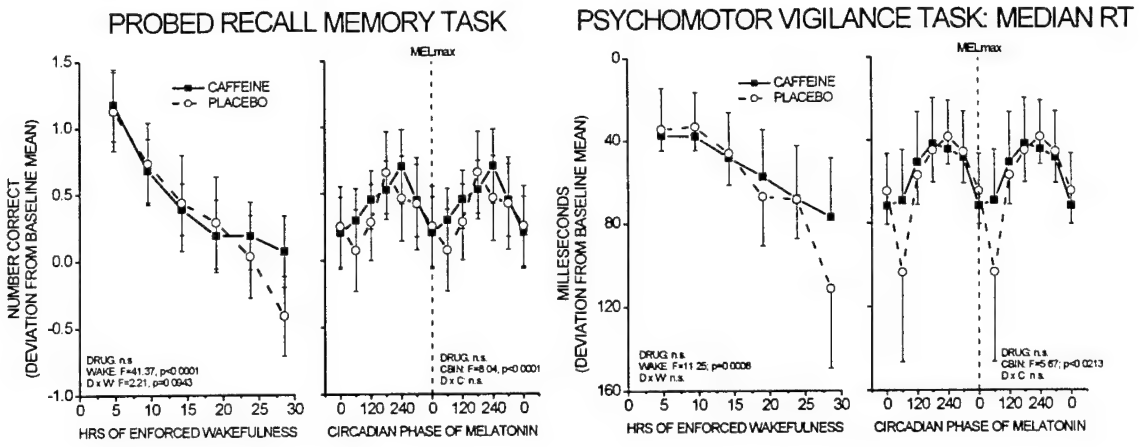
As indicated in the figure (at left), plasma caffeine levels rose in parallel to the hypothesized wake-dependent increase in homeostatic sleep pressure. However, as expected, we did not observe circadian modulation of plasma caffeine levels. In general, caffeine levels built up gradually throughout the course of the protocol, and were not entirely cleared from the plasma at the time of the beginning of subsequent wake episodes.

(3) Results – Neurobehavioral assessments.

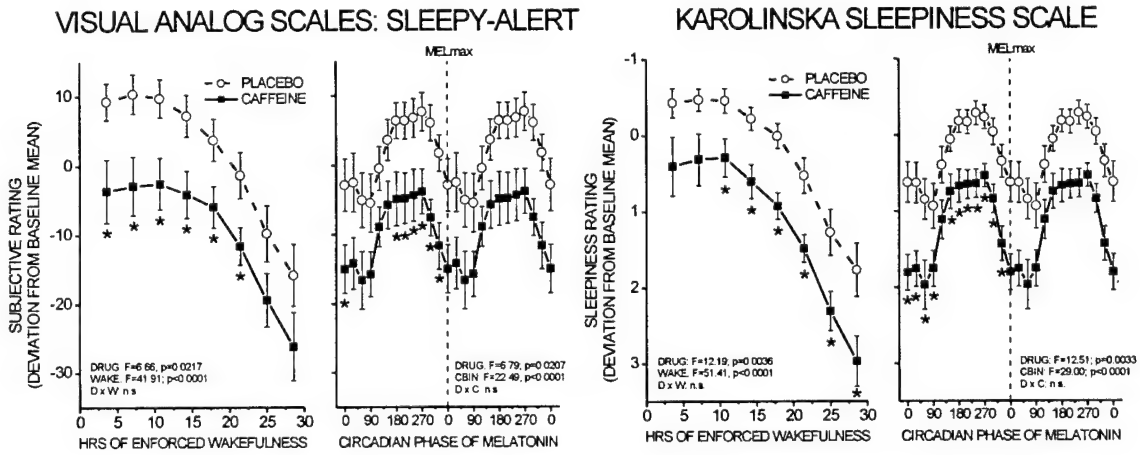


As illustrated in the figures above and below, there was modulation of all neurobehavioral measures based on the duration of prior scheduled wakefulness (left panels) and circadian phase (right panels) for the subjects receiving only placebo during the protocol. However, for the two cognitive throughput tasks (ADD and

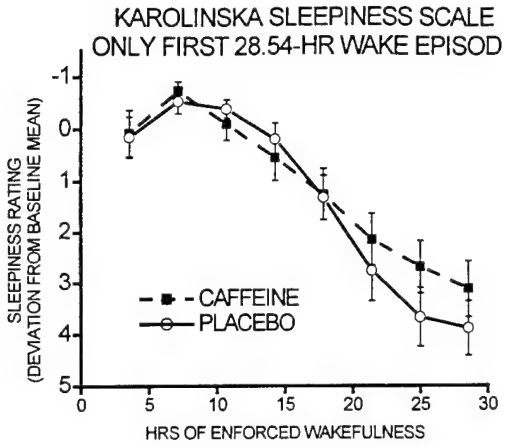
DSST, above), caffeine administration significantly attenuated the wake-dependent impairment of performance. Thus, although subjects in both drug groups began each wake episode with comparable levels of performance, subjects receiving caffeine evidenced very little impairment across these 28.54-hr long wake episodes.

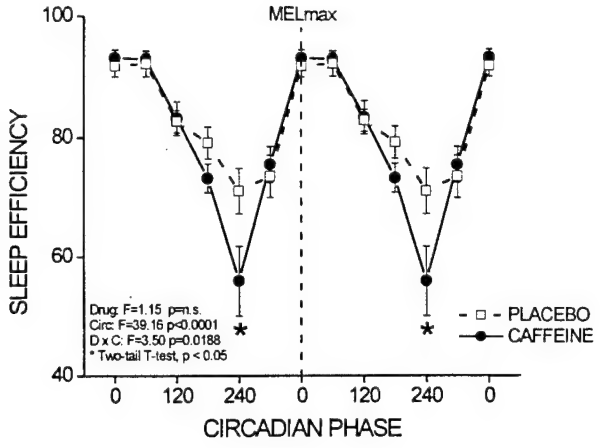


As illustrated in the two figures directly above, caffeine did not appear to significantly impact wake-dependent impairments on the short-term memory (PRM) or psychomotor vigilance tasks (PVT). However, there is suggestive evidence that a beneficial effect of caffeine effect was just beginning to emerge at the end of the wake episodes, which may have become more pronounced with even greater durations of enforced wakefulness, as occurred in the University of Pennsylvania study, where sustained wakefulness episodes in the TSD conditions extended to 88 hours, which is well beyond our 28.56-hr wake episodes.



Regardless of drug condition, subjects rated themselves as more sleepy the longer they were forced to remain awake, and also when wakefulness occurred at the circadian phase just following the maximum of endogenous melatonin secretion. Interestingly, subjects who received caffeine rated themselves as significantly sleepier on two measures of alertness/sleepiness (KSS and VAS, directly above), essentially irrespective of duration of prior wakefulness or circadian phase. To explore this intriguing finding further, we compared the drug conditions for the first wake episodes, when all subjects had been in the laboratory for the preceding three days under normal sleep and wake conditions, and had been receiving only placebo capsules. For only this first long wake episode (see below, left), subjects who received caffeine capsules did not self-report higher levels of sleepiness. This finding reversed itself in subsequent wake episodes, and thus, it is hypothesized that there may be a differential acute versus chronic effect of caffeine administration on waking reports of sleepiness.





(4) Results – Polysomnographic data.

As illustrated above (right figure), caffeine ingestion appeared to significantly decrease sleep efficiency when sleep was scheduled near the minimum of endogenous plasma melatonin secretion. This corresponds to the time interval at the end of the habitual 16-hr wake episode under a normal sleep/wake cycle. Thus, at the time when the intrinsic circadian timing system is maximally promoting wakefulness, caffeine ingestion can add to this wake promoting, sleep impairing effect. This could have important implications for the use of caffeine as a wake promoting therapeutic for round-the-clock operations. The result is consistent with the finding at the University of Pennsylvania site that caffeine reduced sleep efficiency in the NAP + caffeine condition. AT both sites, further analyses are underway to explore potential indications of more subtle sleep disruption related to caffeine, through the use of power spectral analysis of the sleep electroencephalogram recordings.

(5) Further development of biomathematical models of neurobehavioral functions.

Dr. Megan Jewett, Dr. Richard Kronauer and graduate student Daniel Forger have worked extensively to validate the component of the biomathematical model of neurobehavioral function that predicts the effect of light on the human circadian pacemaker that they revised in previous years. This pacemaker model drives the circadian components of alertness and performance in the models of neurobehavioral function. While previous versions of the light model have been unable to accurately predict the response of the human circadian pacemaker to brief stimuli and stimuli of low light intensity, their revised model, consisting of a dynamic light stimulus pre-processor (called *Process L*) and a circadian pacemaker (called *Process P*), can accurately predict a wide range of experimental data, including circadian phase resetting and amplitude suppression. They then went on to identify a simpler (lower-order) set of equations for *Process P* that also could accurately predict the response of the circadian pacemaker to light stimuli. This work was published as three reports in a special issue of the ***Journal of Biological Rhythms, Dec. 1999*** (edited by Drs. Jewett, Czeisler and Borbély). This issue contained the proceedings of an international workshop entitled ***Biomathematical Models of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans, May 1999***, that was organized by Dr. Jewett, chaired by Drs. Czeisler and Borbély, and funded, in part, by the AFOSR. Finally, Mr. Forger, under the supervision of Dr. Kronauer, has developed a preliminary analysis demonstrating that a 10-variable molecular model of the drosophila circadian pacemaker can be mathematically simplified to approximate the features of the validated model of *Process P* for humans. This work was presented at the international meeting of the *Society for Research in Biological Rhythms* in May 2000.

Dr. Megan Jewett has continued to refine and validate her mathematical models of neurobehavioral function. A full description of the development, refinement and validation of mathematical models of subjective alertness and cognitive throughput was published in the special issue of the *Journal of Biological Rhythms, Dec. 1999*. Dr. Jewett has developed a preliminary model of psychomotor vigilance using data collected in the

studies in both Dr. Czeisler's (Harvard) and Dr. Dinges' (University of Pennsylvania) laboratories. This model is able to accurately predict the increase in the number of lapses of attention that occurs during sleep deprivation. Dr. Jewett is currently refining that preliminary model, as well as investigating alternative parameters of the psychomotor vigilance test that may best describe overall performance and assessing the best method to eliminate long-term learning effects from data used in model development. Finally, Drs. Jewett and Kronauer are considering alternate functions to describe the homeostatic effects of sleep and wakefulness on human performance that are mathematically preferable to the current functions (e.g., have a slope > 0 at the maximum, can be easily integrated, etc.) and that better describe the recovery of neurobehavioral function during sleep in cumulative partial sleep deprivation data collected in the laboratory of Dr. David Dinges.

C. Stanford University School of Medicine—Dr. Dale M. Edgar, P.I.

The third set of major research projects undertaken in the Center involved studies on the effects of a number of wake-promoting substances in animal models. This component is vital to the continued identification and development of optimal pharmacological countermeasures to performance-impairing fatigue in Air Force operations. Dr. Edgar and colleagues at the Stanford University School of Medicine completed these projects.

(1) Compensatory sleep responses to drug-induced wakefulness.

Our ongoing studies of wake-promoting therapeutics have included repetitive administration protocols and sustained drug delivery protocols. Both address tolerance and withdrawal issues associated with prolonged use of stimulants involving the dopamine transporter. These studies are critical toward assessing the practical utility of developing selective dopamine reuptake blockers or other somnolytic agents for clinical trials in humans. To establish practical benchmarks, we first evaluated the sleep-wake efficacy of once-weekly treatments of pemoline, GBR12909, methamphetamine and cocaine. Methamphetamine and cocaine are used here as benchmark representatives of drugs with known abuse liability. Each of these drugs retained efficacy (showed little or no tolerance effects) when used in at this frequency. These drugs also exhibited no appreciable wake-promoting sensitization. However early indications suggest that there may be sensitization to the response characteristics of compensatory sleep; that is, repeat administration of dopamine releasing agents (methamphetamine or higher doses of cocaine) may elicit more severe hypersomnolence with repeat administration, even if wake-promoting efficacy remains unaffected or decreases with tolerance. These results point to additional needed studies to assay the safety of somnolytic agents through chronic treatment paradigms. We have initiated chronic treatment studies with cocaine (class example benchmark for drugs of abuse). Cocaine was administered continuously for 7 days via a minipump (10 mg/kg/day and 20mg/kg/day). Sleep-wakefulness was monitored continuously for 21 days using SCORE (see below for a description). Chronic treatment produced wakefulness that resulted in tolerance after 3 days. Upon drug withdrawal, there was no change in NREM sleep, but a marked decrease in REM sleep lasting 3 days. Interestingly, the wake-promoting action of the drug was never compensated through elevated sleep time at any point throughout the study. These data constitute critically important benchmark data on which to preclinically assess the effects of sustained delivery/use of other wake-promoting therapeutics (modafinil, GBR12909, pemoline, etc).

(2) Results – Modafinil mechanism of action.

In the course of our AFOSR sponsored research we have shown that selective dopamine reuptake inhibitors can promote wakefulness without invoking rebound hypersomnolence. In many cases (e.g., GBR12909, pemoline) the NREM sleep displaced by drug-induced wakefulness is never compensated. We therefore created class definitions for "somnolytic" (Edgar 1994) wake-promoting therapeutics. The mechanism of action of modafinil, which also has somnolytic properties, has eluded investigators for some time. Since the only "known" receptor that modafinil binds to involves the dopamine transporter (but with weak binding), we hypothesized that drug action at the transporter, even with weak affinity, could have wake-promoting action. We further postulated that the dopamine transporter was necessary for modafinil, GBR12920, and methamphetamine wake-promoting action, but not for the wake-promoting action of caffeine. To test this

hypothesis we gave each of these drugs to mice that genetically lack functional dopamine transporters (DAT). Modafinil efficacy was completely blocked in the DAT knockout mice. Likewise for GBR12909 and methamphetamine. However caffeine efficacy actually increased (e.g., was more potent) in DAT mice. Taken together, these findings support out hypothesis that (1) modafinil's mechanism of action is mediated by the dopamine transporter, and (2) dopamine and adenosine receptors interact as opposing elements of the opponent process mechanisms of sleep regulation. Dopamine activation of D1 receptors may indeed counteract adenosine's sleep promoting action at adenosine A1 receptors through coupled interactions. Modafinil has an outstanding pharmacodynamic profile and is now indicated for disorders of excessive sleepiness and may have important applications in SUSOPS. This study has been submitted for publication *in J. Neuroscience.* Modafinil is therefore a prime candidate

(3) Results – SCORE-2000.

One of our major objectives in the last 6 months of this research program was to upgrade our SCORE™ technology from a DOS operating system environment to state of the art computer platform. We have completed this effort with the creation of SCORE-2000™. This new pre-clinical sleep-wake bioassay system is fully compatible with our existing SCORE™ Sleep-Wake Bioassay Database and data management systems. The new SCORE-2000 system monitors 16 animals per computer, can ultimately employ up to 5 scoring algorithms simultaneously together with consensus algorithms to make consensus state scoring decisions much the way teams of humans would evaluate data. The new SCORE technology samples EEG and EMG in real time and at 4 times the rate of the older SCORE technology – thus the new SCORE-2000 can do real-time digital filtering and real-time artifact detection. The data collection side of SCORE-2000 operates on top of Linux, using inexpensive entry-level servers with RAID-0 data redundancy. Data redundancy/security is further assured by automatically transferring SCORE data over highly secure (128 bit RSA certified tunneling protocols) to a centralized SCORE Database server. But the real power of the new SCORE-2000 technology derives from its accessibility via the Internet. A SCORE-2000 Linux data collection system (referred to as a "SCORE-2000 node") can be set up as a turn-key system anywhere in the world, while operated form a centralized study control center (e.g., our lab at Stanford). All data from the SCORE-2000 node is visualized in real time via Windows-2000 based SCORE-2000 Monitoring Workstations and appropriately configured Windows-98 notebook systems. As an example, data collection from Black Bears in Fairbanks Alaska can now be fully monitored and controlled as efficiently from Stanford as from the SCORE-2000 console at Fairbanks. SCORE system performance and study protocols can also be *directly* monitored by the Principal Investigator while he/she is traveling to give presentations. This technology is unique, has important implications for centralized pre-clinical and clinical research practices, and will greatly enhance pre-clinical research outreach efforts, all of which should accelerate the process of bring new sleep-wake drugs to the market and identifying sleep-wake side effects in all other drugs.

Recognizing the value of this technology Dr. Edgar, Dr. Mignot, and 3 other colleagues founded a company called Hypnion, Inc. This company is a direct transition of AFOSR-PRET efforts conducted at Stanford University. The company has licensed SCORE™, SCORE-2000™ and the SCORE Sleep-Wake Pharmacology Database (which also constitutes an AFOSR-PRET technology transition to industry).

(4) Results – Photic phase response curve in the Octodon degus.

Studies at Stanford laboratory established that the photic phase response curve in the Octodon degus, a mammal that can exhibit both diurnal and nocturnal activity phase preferences (Kas & Edgar, J. Neuroscience, PRET-sponsored research) are the same as the prototypical PRC for virtually all other organisms. These findings are critically important for the development of novel phase shifting agents or light treatment strategies. This work is now described in a published paper (*Am. J. Physiol.* 278: R1385-R1389, 2000).

(5) Results – Caffeine administration during sleep deprivation.

This study investigated the effects of caffeine on attempts to sleep during sleep deprivation and

subsequent compensatory sleep response. This study has been completed and has been accepted in a peer-reviewed publication (Wurts, SW, and Edgar DM: Caffeine during sleep deprivation: Sleep tendency and dynamics of recovery sleep in rats. *Pharmacol. Biochem. Behav.*, 65: 155-162, 2000). Results show sustained caffeine efficacy toward reducing sleep attempts during the course of sleep deprivation.

(6) Results – Sleep deprivation.

This study has been completed and is described in a published manuscript (*Sleep* 22: 1045-1053, 1999). The research provides evidence for SCN-dependent alerting mechanisms that oppose homeostatic sleep drive in a crepuscular rodent, confirming the generality of "opponent Processes" in mammalian sleep-wake regulation.

(7) Results – Non-photic entrainment in the *Octodon degus*.

This study has been completed and has been accepted for publication in the *Journal of Biological Rhythms*. The study shows that exercise-related non-photic stimuli can have complex interactions on period and phase control.

(8) Results – Light-Dark cycle masking of sleep-wakefulness in the *Octodon degus*.

The purpose of this study was to determine if the activity-dependent reversal of active-phase preference (e.g. reversal from diurnal to nocturnal) reverses the animals' phenotypic masking response to light. Normally light increases activity in diurnal species and inhibits activity in nocturnal species. Our experiments revealed that reversal of activity phase preference could also reverse masking responses, although not in 100% of the animals' studies. Nonetheless, evidence for reversal in masking responses as a function of exercise in Octodon degus confirm our hypothesis that phase preference reversal occurs downstream from the pacemaker (e.g., is mediated by a polarity reversal element in a primary effector relay pathway that does not involve the timing elements of circadian pacemaker). This work has been written up for publication in *Brain Research.*

(9) Results – REM sleep deprivation studies in intact and SCN-lesioned rats.

The purpose of this experiment was to examine the dynamics of REM sleep recovery and potential modulation of this recovery by the circadian system. Intact and SCN-lesioned rats (lesions that experimentally inactivate the circadian time keeping system) were subjected to 24 hours of selective REM sleep deprivation using our unique NOSLEEP sleep-deprivation system (a variant of SCORE™) that was developed and implemented under this AFOSR grant. These studies suggest that, in addition to the well-documented non-REM sleep homeostatic process, a separate REM sleep homeostatic process exists in mammals. The data we have collected to date suggests that the recovery of REM sleep after selective REM sleep deprivation is not gated by the circadian system, however propensity to enter REM sleep during selective REM sleep deprivation is strongly modulated by circadian phase. A comprehensive report on this work is published in *J. Neuroscience* 20: 4300-4310, 2000.

4. PERSONNEL AND TRAINEES (N = 28) SUPPORTED BY CENTER

University of Pennsylvania:

David F. Dinges, Ph.D.	Professor of Psychology in Psychiatry
Shiv Kapoor, Ph.D.	Assistant Professor of Medicine
Martin P. Szuba, M.D.	Assistant Professor of Psychiatry
Janet M. Mullington, Ph.D.*	Post-doctoral Researcher
Naomi Rogers, Ph.D.*	Post-doctoral Researcher
Hans P. A. Van Dongen, Ph.D.*	Post-doctoral Researcher
Melissa M. Mallis, Ph.D.*	Post-doctoral Researcher
John W. Powell, IV, M.A.	Senior Computer/Technology Specialist

Linda Mangino	Program Coordinator (9/99-present)
Barbara R. Barras, M.B.A.	Program Coordinator (1995-8/99)
Marieke Dijkman, M.D.*	Pre-doctoral Trainee
Nicholas Price *	Pre-doctoral Trainee, Biomedical Engineering
Michele M. Carlin	Research Associate, Project Manager
Emily Carota Orne	Research Associate
Kelly A. Gillen, RPSGT	Physiological Monitoring Coordinator
Claire G. Brodnyan, RPSGT	Physiological Monitoring Coordinator
Christine M. Dinges	Research Associate
Sharon Kelley	Research Associate
Jennifer Law*	Research Associate
Matthew Martino*	Research Associate
Nicole Konowal*	Undergraduate Honors Student/Behavioral Monitor
Angela Kuo*	Undergraduate Honors Student/Behavioral Monitor
Natalie Denney*	Undergraduate Student/Behavioral Monitor
Judd Flesch*	Undergraduate Student/Behavioral Monitor
Beatrice Jauregui*	Undergraduate Student/Behavioral Monitor
Sofiya Kuchuk*	Undergraduate Student/Behavioral Monitor
Erica Levine*	Undergraduate Student/Behavioral Monitor
Lucy MacGillis*	Undergraduate Student/Behavioral Monitor

Harvard University:

Charles A. Czeisler, Ph.D., M.D.	Professor of Medicine
Richard E. Kronauer, Ph.D.	Professor of Applied Mathematics
Derk-Jan Dijk, Ph.D.	Assistant Professor of Medicine
Christian Cajochen, Ph.D.*	Instructor in Medicine
Rod J. Hughes, Ph.D.	Instructor in Medicine
Megan E. Jewett, Ph.D.*	Instructor in Medicine
James K. Wyatt, Ph.D.*	Instructor in Medicine
Kenneth Wright, Ph.D.*	Post-doctoral Researcher
Joseph M. Ronda, M.S.	Computer Systems Manager
Angela Ritz-DeCecco, M.S.*	Research Graduate Student
Ralph Todesco	Operations Manager
Lisa DiFabio	Administrative Secretary
Karen O'Hagen	Office Assistant
Wendy Campanella	Research Assistant
Sara Den Besten	Research Assistant
Sara Dineen	Research Assistant
Johnette Kao	Research Assistant
David Rimmer	Research Assistant
Eymand Reil	Sleep EEG Analysis Research Assistant
Val Saxe	Chief Technician
Gerald Jayne	Senior Research Technician
Lisa Bocelli	Technical Research Assistant
Brian Cade	Technical Research Assistant
Dorothy Chen	Technical Research Assistant
Deirdre Conroy	Technical Research Assistant
Theresa Kelly	Technical Research Assistant
Anthony Monacelli	Technical Research Assistant

Patricia Poladori	Technical Research Assistant
Jason Sullivan	Technical Research Assistant
John Whittemore	Technical Research Assistant
Zachery Zichitella	Technical Research Assistant
Edward Silva	Data Coordinator
David Wachs*	Undergraduate Student/Research Assistant

Stanford University:

Dale M. Edgar, Ph.D.	Associate Professor & Stanford AFOSR-PRET P.I.
William C. Dement, M.D., Ph.D.	Professor of Psychiatry & Behavioral Sciences
Emmanuel Mignot, M.D., Ph.D.	Associate Professor of Psychiatry & Behavioral Sci.
Seiji Nishino, Ph.D.	Senior Research Scientist
Margaret J. Bradbury, Ph.D.*	Post-doctoral Researcher
Foster Olive, Ph.D.*	Post-doctoral Researcher
Jonathan P. Wisor, Ph.D.*	Post-doctoral Researcher
Sarah (Sally) Wurts, Ph.D.*	Doctoral Student (Sleep & Circadian Neurobiology)
Martien Kas, Ph.D.*	Doctoral Student (Sleep & Circadian Neurobiology)
Laura Alexander	SCORE Animal Health Technician
Sonia Baragan	Research Administration
Katy Filikova	Research Administration
Pamela Hyde	Research Administration Manager
Tela Roche	Research Administration
Susan Wise	Assistant to Professor Edgar 3/97-6/97
Humberto Garcia	SCORE Animal Surgery and Treatment
Wesley Seidel	SCORE Bioassay and Database Manager
Ronny Tjon	Electronics and Computer Technician
Mark Sergott	Research and Database Assistant
Irene Linetskaya*	Undergraduate Student/Research Assistant

***PRET Center Trainees (total N = 28)**

5. LIST OF CENTER PUBLICATIONS

5A. 1995-2000 TOTAL N = 93 JOURNAL ARTICLES, CHAPTERS, REVIEWS, DISSERTATIONS SUPPORTED IN WHOLE OR IN PART BY THE CENTER

1995 (n = 3) Journal articles, chapters, reviews, dissertations

Dinges, D.F.: An overview of sleepiness and accidents. *Journal of Sleep Research, 4-S2*: 4-14, 1995.

Edgar, D.M.: Control of sleep-wake cycles by the mammalian suprachiasmatic pacemaker. *SRS Bulletin, 1:* 2-7, 1995a.

Edgar, D.M.: In search of neurobiological mechanisms regulating sleep-wakefulness: An empirical and historical account of two opponent processes. *SRS Bulletin, 1:* 22-27, 1995b.

1996 (n = 4) Journal articles, chapters, reviews, dissertations

Dijk, D-J.: Internal rhythms in humans. *Seminars in Cell and Developmental Biology*, 7:831-836, 1996.

Edgar, D.M.: Circadian control of sleep/wakefulness: Implications in shift work and therapeutic strategies. In: K. Shiraki, S. Sagawa., and M.K.Yousef (Eds.), *Physiological Basis of Occupational Health: Stressful Environments.* Amsterdam: SPB Academic Publishing, pp. 253-265, 1996.

Gary, K.A., Winokur, A., Douglas, S.D., Kapoor, S., Zaugg, L., and Dinges, D.F.: Total sleep deprivation and the thyroid axis: Effects of sleep and waking activity. *Aviation, Space, and Environmental Medicine*, 67(6): 513-519, 1996.

Heller, H.C., Edgar, D.M., Grahn, D.A., and Glotzbzch, S.F.: Sleep, thermoregulation, and circadian rhythms. In MJ Fregly and CM Blatteis (Eds.), *Handbook of Physiology Section 4, Environmental Physiology Vol II. American Physiological Society*. New York: Oxford University Press, pp. 1361-1374, 1996.

1997 (n = 24) Journal articles, chapters, reviews, dissertations

Boivin, D.B., Czeisler, C.A., Dijk, D-J, Duffy, J.F., Folkard, S., Minors, D.S., Totterdell, P., and Waterhouse, J.M.: Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. *Archives of General Psychiatry, 54*:145-152, 1997.

Bradbury, M.J., Dement, W.C., and Edgar, D.M.: Serotonin-containing fibers in the suprachiasmatic hypothalamus attenuate light-induced phase delays in mice. *Brain Research, 768*:125-134, 1997.

Brown, E.N., Choe, Y., Shanahan, T.L., and Czeisler, C.A.: A mathematical model of diurnal variations in human plasma melatonin levels. *American Journal of Physiology, 272*:E506-E516, 1997.

Czeisler, C.A.: Commentary: Evidence for melatonin as a circadian phase shifting agent. *Journal of Biological Rhythms, 12*:618-623, 1997.

Czeisler, C.A., and Richardson, G.S.: Disorders of sleep and circadian rhythms. In: A.S. Fauci, E. Braunwald, K.J. Isselbacher, J.D. Wilson, J.B. Martin, D.L. Kasper, et al. (Eds.), *Harrison's principles of internal medicine* (14th ed). NewYork: McGraw-Hill, Inc., pp. 150-159, 1997.

Czeisler, C.A., and Turek, F.W. (Eds.), *Controversies in melatonin therapy. Special issue of the Journal of Biological Rhythms*. Thousand Oaks, CA: Sage Science Press, 1997.

Dijk, D-J.: Light, circadian rhythms and the homeostatic regulation of human sleep. In J.M. Kinney and H.N. Tucker (Eds.), *Physiology, Stress and Malnutrition*. New York: Lippincott-Raven Publishers, pp. 55-78, 1997.

Dijk, D-J and Cajochen, C.: Melatonin and the circadian regulation of sleep initiation, consolidation, structure and the sleep EEG. *J. Biol. Rhythms*, *12*:627-635, 1997.

Dijk, D-J. and P. Lavie: Review of the rhythms of human sleep propensity and core body temperature by L.C. Lack and K. Lushington. *Sleep Research*, *26*:763,773, 1997.

Dijk, D.J., Shanahan, T.L., Duffy, J.F., Ronda, J.M., and Czeisler, C.A.: Variation of electroencephalographic activity during non-rapid eye movement sleep with phase of circadian melatonin rhythm in humans. *Journal of Physiology* (London), *505.3*:851-858, 1997.

Dijk, D-J.: Physiology of sleep homeostasis and its circadian regulation. In W.J. Schwartz (Ed.), *Sleep Science: Integrating Basic Research and Clinical Practice*. Karger, Basel, pp. 10-33, 1997.

Dinges, D.F.: The promise and challenges of technologies for monitoring operator vigilance. *Proceedings of the International Conference on Managing Fatigue in Transportation.* Tampa, Fl: American Trucking Foundation, pp. 77-86, 1997.

Dinges, D.F. and Chugh, D.K.: Physiologic correlates of sleep deprivation. In J.M. Kinney (Ed.), *Physiology, stress and malnutrition.* New York: Lippincott-Raven, pp. 1-27, 1997.

Dinges, D.F., Pack, F., Williams, K., Gillen, K.A., Powell, J.W., Ott, G.E., Aptowicz, C., and Pack, A.I.: Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep, 20(4):*267-277, 1997.

Edgar, D.M.: Tinkering with the circadian clock. *Stanford Medicine, 15(1):* 7-32, 1997.

Edgar, D.M., Reid, M.S., and Dement, W.C.: Serotonergic afferents mediate activity-dependent entrainment of the mouse circadian clock. *American Journal of Physiology, 42*:R265-R269, 1997.

Edgar, D.M., and Seidel, W.F.: Modafinil induces wakefulness without intensifying motor activity or subsequent rebound hypersomnolence in the rat. *J. Pharmacol. Exp. Ther., 283*:757-769, 1997.

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Jewett, M.E., Rimmer, D.W., Duffy, J.F., Klerman, E.B., Kronauer, R.E., Czeisler, C.A.: Human circadian pacemaker is sensitive to light throughout subjective day without evidence of transients. *American Journal of Physiology, 273*:R1800-1809, 1997.

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Shanahan, T.L., Zeitzer, J.M., and Czeisler, C.A.: Resetting the melatonin rhythm with light in humans. *Journal of Biological Rhythms, 12*:556-567, 1997.

Smith-Coggins, R., Rosekind, M.R., Buccino, K.R., Dinges, D.F., and Moser, R.P.: Rotating shiftwork schedules: Can we enhance physician adaptation to night shifts? *Academic Emergency Medicine, 4*:951-961, 1997.

Zeitzer, J.M., Kronauer, R.E., and Czeisler, C.A.: Photopic transduction implicated in human circadian entrainment. *Neuroscience Letters, 232*:135-138, 1997.

1998 (n = 12) Journal articles, chapters, reviews, dissertations

Boivin, D.B. and Czeisler, C.A.: Resetting of circadian melatonin and cortisol rhythms in humans by ordinary room light. *Neuroreport, 9*:779-782, 1998.

Bradbury, M.J., Dement, W.C., and Edgar, D.M.: Effects of adrenalectomy and subsequent corticosterone treatment on rat sleep state and EEG power spectra. *American Journal of Physiology, 275*:R555-R565, 1998.

Dinges, D.F., and Mallis, M.M.: Managing fatigue by drowsiness detection: Can technological promises by realized? In: L. Hartley (Ed.), *Managing Fatigue in Transportation.* Proceedings of the 3rd International Conference on Fatigue in Transportation. Pergamon, Oxford, pp.209-229, 1998.

Duffy, J.F., Dijk, D-J., Klerman, E.B., and Czeisler, C.A.: Later endogenous circadian temperature nadir relative to an earlier wake time in older people. *American Journal of Physiology 275:*R1478-R1487, 1998.

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Kronauer, R.E., Jewett, M.E., and Czeisler, C.A.: Modeling human circadian phase and amplitude resetting. In: Y. Touitou (Ed.), *Biological clocks: Mechanisms and applications.* Elsevier Science, B.V., pp. 63-72, 1998.

O'Hara, B.F., Cao, V.H., Wiler, S.W., Heller, H.C., Edgar, D.M., Kilduff, T.S., and Miller, J.D.: Nicotine and nicotine receptors in the SCN. *Psychoneuroendocrinology 23*: 161-173, 1998.

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Van Dongen, H.P.A., Mullington, J.M., Dinges, D.F.: Circadian phase delay during 88-hour sleep deprivation in dim light: differences among body temperature, plasma melatonin and plasma cortisol. *Sleep-Wake Research in the Netherlands, 9:*33-36, 1998.

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Cajochen, C., Khalsa, S.B.S., Wyatt, J.K., Czeisler, C.A., Dijk, D-J.: EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. *Am. J. Physiol., 277:*R640-R649, 1999.

Czeisler, C.A., Dijk, D-J., Neri, D.F., Hughes, R.J., Ronda, J.M., Wyatt, J.K., West, J.B., Prisk, G.K., Elliott, A.R., Young, L.R.: Ambient light intensity, actigraphy, sleep and respiration, circadian temperature and melatonin rhythms and daytime performance of crew members during space flight on STS-90 and STS-95 missions. *First Biennial Space Biomedical Investigators' Workshop.* p. 544-546, 1999.

Czeisler, C.A., Duffy, J.F., Shanahan, T.L., Brown, E.N., Mitchell, J.F., Rimmer, D.W., Ronda, J.M., Silva, E.J., Allan, J.S., Emens, J.S., Dijk, D-J., Kronauer, R.E.: Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science, 284:*2177-2181, 1999.

Czeisler, C.A., and Wright, Jr, K.P.: Influence of light on circadian rhythmicity in humans. In: F.W. Turek and P.C. Zee (Eds.), *Neurobiology of sleep and circadian rhythms* (for series on Lung Biology in Health and Disease). New York: Marcel Dekker, Inc., pp. 147-180, 1999.

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Dijk, D-J.: Circadian variation of EEG power spectra in NonREM and REM sleep in humans: Dissociation from body temperature. *Journal of Sleep Research, 8(3):* 189-195, 1999.

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Dinges, D.F., and Achermann, P.: Future considerations for models of human neurobehavioral function. *Journal of Biological Rhythms, 14(6):* 598-601, 1999.

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Forger, D.B., Jewett, M.E., Kronauer, R.E.: A simpler model of the human circadian pacemaker. *Journal of Biological Rhythms, 14*:532-537, 1999.

Jewett, M.E., Borbély, A.A., Czeisler, C.A.: Editorial: Biomathematical modeling workshop, May 18-21, 1999. *Journal of Biological Rhythms, 14*:429-430, 1999.

Jewett, M.E., Dijk, D-J, Kronauer, R.E., and Dinges, D.F.: Dose response relationship between sleep duration and human psychomotor vigilance and subjective alertness. *Sleep 22(2):*171-179, 1999.

Jewett, M.E., Forger, D.B., Kronauer, R.E.: Revised limit cycle oscillator model of the human circadian pacemaker. *Journal of Biological Rhythms, 14*:493-499, 1999.

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Jewett, M.E., Wyatt, J.K., Ritz-De Cecco, A., Khalsa, S.B., Dijk, D-J, and Czeisler, C.A.: Time course of sleep inertia dissipation in human performance and alertness. *J.Sleep Res. 8*:1-8, 1999.

Kas, M.H., and Edgar, D.M.: A non-photic stimulus inverts the diurnal-nocturnal phase preference in *Octadon degus. J. Neuroscience, 19(1):*328-333, 1999.

Kas, M.J.H., and Edgar, D.M.: Circadian timed wakefulness at dawn opposes compensatory sleep responses after sleep deprivation in *Octodon degus. Sleep 22(8):*1045-1053, 1999.

Kas, M.J.H., and Edgar, D.M.: Crepuscular timed wakefulness at dawn opposes compensatory sleep responses after sleep deprivation in *Octadon degus. Sleep, 22*:1045-1053, 1999.

Kelly, T.L., Neri, D.F., Grill, J.T., Ryman, D., Hunt, P.D., Dijk, D-J., Shanahan, T.L., Czeisler, C.A.: Nonentrained circadian rhythms of melatonin in submariners scheduled to an 18-hour day. *Journal of Biological Rhythms, 14(3):*190-196, 1999.

Khalsa, S.B.S. and Dijk, D-J.: Melatonin as a countermeasure for entrainment to the sleep/wake schedules required during shuttle missions. *First Biennial Space Biomedical Investigators' Workshop.* p. 555-558, 1999.

Klerman, E.B., Boulos, Z., Edgar, D.M., Mistlberger, R.E., Moore-Ede, M.C.: Circadian and homeostatic influences on sleep in the squirrel monkey: sleep after sleep deprivation. *Sleep, 22(1):*45-59, 1999.

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Turek, F.W., and Czeisler, C.A.: Role of melatonin in the regulation of sleep. In: F.W. Turek and P.C. Zee (Eds.), *Neurobiology of sleep and circadian rhythms* (for series on Lung Biology in Health and Disease). New York: Marcel Dekker, Inc., pp. 181-195, 1999.

Van Dongen, H.P.A., Olofsen, E., VanHartevelt, J.H., Kruyt, E.W.: Searching for biological rhythms: peak detection in the periodogram of unequally spaced data. *Journal of Biological Rhythms, 14(6)*:617-620, 1999.

Van Dongen, H.P.A., and VanHartevelt, J.H.: A procedure of multiple period searching in unequally spaced time-series with the Lomb-Scargle method. *Biological Rhythm Research, 30(2)*:149-177, 1999.

Vanover, K.E., Edgar, D.M., Seidel, W.F., Hogenkamp, D.J., Fick, D.B., Lan, N.C., Gee, K.W., Carter, R.B.: Response rate suppression in an operant paradigm as a predictor of soporific potency in rats and the identification of three novel sedative-hypnotic neuroactive steroids. *J. Pharmacol. Exp. Ther., 291:*1317-1323, 1999.

Wei, H.G., Riel, E., Czeisler, C.A., Dijk, D-J.: Attenuated amplitude of circadian and sleep-dependent modulation of electroencephalographic sleep spindle characteristics in elderly human subjects. *Neuroscience Letters, 260:*29-32, 1999.

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Zeitzer, J.M., Daniels, J.E., Duffy, J.F., Klerman, E.B., Shanahan, T.L., Dijk, D-J., Czeisler, C.A.: Do plasma melatonin secretions decline with age? *American Journal of Medicine, 107(5)*:432-436, 1999.

2000, in press, and submitted manuscripts (n = 17) Journal articles, chapters, reviews, dissertations

Czeisler, C.A., and Khalsa, S.B.: The human circadian timing system and sleep-wake regulation. In: M.H. Kryger, T. Roth, and W.C. Dement (Eds.), *Principles and Practices of Sleep Medicine* (3rd Edition). Orlando, Florida: W.B. Saunders, pp. 353-375, 2000.

Doran, S.M., Van Dongen, H.P.A., Dinges, D.F.: Sustained attention performance during sleep deprivation: evidence of state instability. *Archives of Italian Biology,* in press.

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Kaş, M.H., and Edgar, D.M.: Photic phase response curve in *Octadon degus*: assessment as a function of activity phase preference. *American Journal of Physiology, 278*:R1385-R1389, 2000.

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Klerman, E.B., Boulos, Z., Edgar, D.M., Mistlberger, R.E., Moore-Ede, M.C.: EEG delta activity during undisturbed sleep in the squirrel monkey. *Sleep Research Online,* in press.

Rogers, N.L., Kennaway, D.J., Dawson, D.: Neurobehavioral performance effects of daytime melatonin and temazepam administration. submitted.

Shearer, W.T., Reuben, J.M., Mullington, J.M., Price, N.J., Lee, B.N., Smith, E.O., Szuba, M.P., Van Dongen, H.P.A., Dinges, D.F.: Plasma sTNF-RI and IL-6 levels in humans subjected to the sleep deprivation model of space flight. *Journal of Allergy and Clinical Immunology,* in press.

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Van Dongen, H.P.A., and Dinges, D.F.: Circadian rhythms in fatigue, alertness and performance. In: M.H. Kryger, T. Roth, and W.C. Dement (Eds.), *Principles and Practices of Sleep Medicine* (3rd Edition). Orlando, Florida: W.B. Saunders, pp. 391-399, 2000.

Van Dongen, H.P.A., Brodnyan, C.G., MacAdam, H.L., Dinges, D.F.: Sleep architecture of nighttime and daytime naps during 88 hours of extended wakefulness. *Sleep-Wake Research in The Netherlands 11,* in press.

Van Dongen, H.P.A., and Kerkhof, G.A.: Repeated assessment of the endogenous 24-hour profile of blood pressure under constant routine. *Chronobiology International,* submitted.

Van Dongen, H.P.A., Price, N.J., Mullington, J.M., Szuba, M.P., Kapoor, S.C., Dinges, D.F.: Caffeine eliminates sleep inertia after awakening from reduced sleep. submitted.

Wisor, J.P., and Edgar, D.M.: Genetically and temporally distinct compensatory sleep responses in mice. submitted.

Wisor, J.P., Nishino, S., Sora, I., Uhl, G.H., Mignot, E., Edgar, D.M.: Sleep regulation and response to stimulants is impaired in DAT knockout mice. submitted.

Wurts, S.W., and Edgar, D.M.: Circadian and homeostatic control of rapid eye movement (REM) sleep: Promotion of REM tendency by the suprachiasmatic nucleus. *The Journal of Neuroscience, 20(11)*:4300-4310, 2000.

Wurts, S.W., and Edgar, D.M.: Caffeine during sleep deprivation: sleep tendency and dynamics of recovery sleep in rats. *Pharmacology Biochemistry and Behavior, 65(1)*:155-162, 2000.

5B. 1995-2000 TOTAL N = 87 ABSTRACTS SUPPORTED IN WHOLE OR IN PART BY THE CENTER

1995 (n = 4) Abstracts

Edgar, D.M., Seidel, W.F., Bradbury, M.J., and Dement, W.C.: Sleep bout-length, non-REM sleep time, and EEG delta power as indices of compensatory responses to sleep deprivation. *Sleep Research, 24A*: 430, 1995.

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Edgar, D.M., Seidel, W.F., Dement, W.C., and Mignot, E.: Low-dose treatment with the selective dopamine uptake blocker GBR-12909 increases wakefulness without intensifying motor activity in the rat. *Soc. Neuroscience Abst., 21*: 180, 1995.

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Dinges, DF: Estimating homeostatic and circadian interaction during sleep deprivation: Mood versus performance? *Journal of Sleep Research*, 5(supplement 1), 50, 1996.

Edgar, D.M., Kas, M.J.H., Bradbury, M.J., and Dement, W.C.: Is NPY necessary for activity-dependent entrainment in the mouse? *Soc. Res. Biol. Rhythms Abstracts, 106*: 80, 1996.

Jewett, M.E., Dijk, D-J., Kronauer, R.E., Boivin, D.B., and Czeisler, C.A.: Homeostatic and circadian components of subjective alertness interact in a non-addictive manner during 48 hours of sleep deprivation. *Journal of Sleep Research, 5-S1*: 101, 1996.

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Kronauer, R.E., Jewett, M.E., Dijk, D-J., and Czeisler, C.A.: A model for reduced circadian modulation of alertness at extremes of homeostatic influence. *Journal of Sleep Research, 5-S1*: 113, 1996.

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Seidel, W.F., Dement, W.C., and Edgar, D.M.: NonREM sleep in rats after various wake-promoting agents. *Sleep Research, 25*: 478, 1996.

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Dijk, D-J, Shanahan, T.L., and Czeisler, C.A.: Individual differences and non-additive effect of rest-activity cycle and melatonin phase on core body temperature. *Sleep Research, 26*:709, 1997.

Dijkman, M., Sachs, N., Levine, E., Mallis, M., Carlin, M.M., Gillen, K.A., Powell, J.W., Samuel, S., Mullington, J., Rosekind, M.R., Dinges, D.F.: Effects of reduced stimulation on neurobehavioral alertness depend on circadian phase during human sleep deprivation. *Sleep Research, 26*: 265, 1997.

Hall, E.F., Duffy, J.F., Dijk, D-J, and Czeisler, C.A. Interval between waketime and circadian phase differs between morning and evening types. *Sleep Research, 26*:716, 1997.

Kas, M.J.H., Dement, W.C., and Edgar, D.M.: Sleep-Wake architecture in a diurnal rodent, *Octadon degus. Sleep Research, 26*: 721, 1997.

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Mullington, J., Hermann, D., and Pollmacher, T.: Soluble TNF receptor P55 is elevated at night due to circadian variation. *Sleep Research, 26*: 741, 1997.

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Rosekind, M.R., Gregory, K.B. Miller, D.L., Oyung, R.L., Neri, D.F., Dinges, D.F.: Sleep quantity and quality of augmented long-haul flight crews in on-board crew rest facilities. *Sleep Res.* 26:41, 1997.

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Wyatt, J.K., Dijk, D-J, and Czeisler, C.A.: Sleep structure and neurobehavioral performance in a 20-HR forced desynchrony protocol: Sleep/wake homeostatic and circadian modulation. *Sleep, 21*:244, 1998.

1999 (n = 26) Abstracts

Barnes, B.M., Tøien, Ø., Blake, J., Grahn, D., Heller, H.C., Edgar, D.M.: Hibernation in black bears: body temperature cycles and sleep. *FASEB J. 13*: A740, 1999.

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Dinges, D.F., Shearer, W.T., Reuben, J.M., Mullington, J.M., Price, N., Szuba, M.P., Kapoor, S., Van Dongen, H.P.A.: Human immune status during prolonged sleep deprivation: circadian rhythmicity, sleep drive, stress, and caffeine. *Sleep Research Online 2(Suppl. 1):*659, 1999.

Edgar, D.M. and Seidel, W.F.: Modafinil-induced wakefulness is attenuated in medial HDB-lesioned but not SCN-lesioned rats. *Sleep Research Online 2(Suppl. 1):*137, 1999.

Jewett, M.E., Dijk, D-J., Kronauer, R.E., Czeisler, C.A.: Sigmoidal decline of homeostatic component in subjective alertness and cognitive throughput. *Sleep, 22S*: S94, 1999.

Jewett, M.E., Wyatt, J.K., Ritz-De Cecco, A., Dijk, D-J., Khalsa, S.B.S., Czeisler, C.A.: Cognitive throughput and subjective alertness after awakening: investigation of sleep inertia with respect to three different circadian phases. *Sleep, 22S*: S88, 1999.

Kas, M.J.H. and Edgar, D.M.: Entrainment and masking of sleep-wakefulness and body temperature circadian rhythms in *Octodon degus*. *Sleep Research Online 2(Suppl. 1):*608, 1999.

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Mallis, M.M., Maislin, G., Powell, J.W., Dinges, D.F.: Effects of auditory-vibrotactile alerts on performance in sleepy subjects. *Sleep, 22S*: S299, 1999.

Mallis, M.M., Maislin, G., Powell, J.W., Konowal, N.M., Dinges, D.F.: PERCLOS predicts both PVT lapse frequency and cumulative lapse duration. *Sleep, 22S*: S149, 1999.

Mullington, J.M., Carlin, M.M., Kapoor, S., Iftaker, S., Samuel, S., Price, N., Szuba, M.P., Dinges, D.F.: Sleep deprivation elevates the circadian nadir in cortisol secretion. *Sleep, 22S*: S329, 1999.

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Ritz-De Cecco, A., Jewett, M.E., Wyatt, J.K., Kronauer, R.E., Czeisler, C.A., Dijk, D-J.: Plasma melatonin rhythm in humans during a 20-h forced desynchrony protocol. World Federation of Sleep Research Societies conference, Dresden, Germany. October, 1999.

Seidel, W., and Edgar, D.M.: Cocaine and compensatory sleep. *Sleep, 22S:*S340, 1999.

Seidel, W.F. and Edgar, D.M.: Dopamine reuptake blockers and compensatory sleep. *Sleep Research Online 2(Suppl. 1):*167, 1999.

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Tøien, Ø., Barnes, B.M., Blake, J., Grahn, D., Heller, H.C., Edgar, D.M.: Hibernation in black bears: energetics and thermoregulation. *FASEB J. 13*: A740, 1999.

Van Dongen, H.P.A. and Dinges, D.F.: Circadian phase drift during 3.5 days of sleep restriction in dim light. *Proceedings of the International Congress on Chronobiology,* Washington, D.C.,: 86, August 28-September 1, 1999.

Van Dongen, H.P.A. and Dinges, D.F.: Caffeine as a performance enhancing drug in Air Force operations. *Proceedings of the Seventieth Anniversary Annual Scientific Meeting of the Aerospace Medical Association,* Detroit, Michigan: 50, May 16-20, 1999.

Van Dongen, H.P.A., Olofsen, E., VanHartevelt, J.H., Kruyt, E.W.: Power spectral analysis: generalizing the invariance to time translation. *Poster abstracts of the Workshop on Biomathematical Models of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans,* Dedham, Massachusetts: 3, May 18-21, 1999.

Van Dongen, H.P.A., Powell, J.W., Konowal, N.M., Brodnyan, C.G., Mullington, J.M., Dinges, D.F.: The dynamics of chronically restricted sleep and recovery sleep. *Sleep, 22S*: S116-S117, 1999.

Wişor, J.P. and Edgar, D.M.: Genetic and temporal segregation of sleep homeostatic processes in mice. *Sleep Research Online 2(Suppl. 1):*562, 1999.

Wurts, S.W. and Edgar, D.M.: EEG power spectra after REM sleep deprivation in sham and SCN-lesioned rats. *Sleep Research Online 2(Suppl. 1):*563, 1999.

Wyatt, J.K., Dijk, D-J., Ritz-De Cecco, A., Czeisler, C.A.: Circadian phase-dependent hypnotic effect of exogenous melatonin. *Sleep, 22S*: S4, 1999.

2000, in press (n = 14) Abstracts

Benke, K.S., Jewett, M.E., Kalsa, S.B.S., Czeisler, C.A.: Hourly and 30-minute sampling: similar phase, duration and amplitude estimates for plasma melatonin. *Sleep*:A374-A375, 2000.

Benke, K.S., Jewett, M.E., Kalsa, S.B.S., Czeisler, C.A.: Decreased sampling rates may provide acceptable melatonin phase, duration and amplitude estimates, depending on the precision required. Abstracts, 7th Meeting, Society for Research on Biological Rhythms, 2000.

Dinges, D.F., Doran, S.M., Mullington, J.M., Van Dongen, H.P.A., Price, N., Samuel, S., Carlin, M.M., Powell, J.W., Mallis, M.M., Martino, M., Brodnyan, C., Konowal, N., Szuba, M.P.: Neurobehavioral effects of 66 hr of sustained low-dose caffeine during 88 hr of total sleep deprivation. *Sleep,* 23(Suppl.2): A20-A21, 2000.

Doran, S.M., Van Dongen, H.P.A., Powell, J.W., Mallis, M.M., Konowal, N., Dinges, D.F.: Effects of cumulative workload on vigilance decrement during total sleep deprivation. *Sleep,* 23(Suppl.2): A240-A241, 2000.

Edgar, D.M. and Seidel, W.F.: Pemoline-induced wakefulness and compensatory sleep: assessment of sensitization and tolerance. *Sleep, 23(suppl#2)*:A252, 2000.

Kas, M.J.H. and Edgar, D.M.: Photic phase response curve and light-dark masking of circadian rhythms in *Octodon degus*: assessment as a function of activity phase preference. *Society for Research on Biological Rhythms Abstracts,* 2000.

MacAdam, H.L., Van Dongen, H.P.A., Brodnyan, C.G., DeBrunier, A., Dinges, D.F.: Effects of 66h of sustained low-dose caffeine on prophylactic naps during 88h of continuous operations. *Sleep,* 23(Suppl.2): A119-A120, 2000.

Price, N., Mullington, Kapoor, S., Samuel, S., Szuba, M.P., Dinges, D.F.: Plasma norepinephrine during 66 hr of sustained low-dose caffeine intake and 88 hr of sleep deprivation. *Sleep,* 23(Suppl.2): A119, 2000.

Rogers, N.L., Price, N., Mullington, J.M., Kapoor, S., Samuel, S., Szuba, M.P., Dinges, D.F.: Effect of repeated caffeine administration on core body temperature during 88 hours of sustained wakefulness. Society for Research on Biological Rhythms, Amelia Island Plantation, Florida, May 2000.

Seidel, W.F. and Edgar, D.M.: Cocaine sensitization versus tolerance. *Sleep, 23(suppl#2)*:A149, 2000.

Terao, A., Peyron, C., Ding, J., Edgar, D.M., Heller, H.C., Kilduff, T.S.: Prepro-hypocretin (prepro-orexin) levels are unaffected by short-term sleep deprivation in rats and mice. *Sleep, 23(suppl#2)*:A94, 2000.

Van Dongen, H.P.A., Doran, S.M., MacAdam, H.L., Szuba, M.P., Dinges, D.F.: Sleep inertia: effects of homeostatic drive, circadian rhythm, and caffeine. *Journal of Sleep Research, 9(Suppl.1)*: 2000.

Van Dongen, H.P.A., Doran, S.M., Mullington, J.M., Powell, J.W., MacAdam, H.L., Szuba, M.P., Dinges, D.F.: Sustained low-dose caffeine administration reduces sleep inertia after nap sleep during 88h extended wakefulness. *Sleep, 23(Suppl.2):* A120-A121, 2000.

Wisor, J.P. and Edgar, D.M.: Genetic influences on methamphetamine-induced compensatory sleep in mice. *Sleep, 23(suppl#2)*:A62, 2000.

5C. 1995-2000 Total N = 6 MANUALS AND TECHNICAL REPORTS SUPPORTED IN PART BY THE CENTER

Dinges, D.F.: Technology/scheduling approaches. In: *Fatigue Symposium Proceedings of the NTSB/ NASA*, pp. 53-58, 1995.

Dinges, D.F.: Performance effects of fatigue. In: *Fatigue Symposium Proceedings of the NASA*, pp. 41-46, 1995.

Dinges, D.F.: Napping strategies. In: *Fatigue Symposium Proceedings of the NTSB/NASA*, pp. 47-51, 1995.

Dinges, DF, Graeber, RC, Rosekind, MR, Samel, A and Wegmann, HM: Principles and guidelines for duty and rest scheduling in commercial aviation. *NASA Technical Memorandum*, May 1996.

Dinges, D.F., Mallis, M., Maislin, G., Powell, J.W.: Evaluation of techniques for ocular measurement as an index of fatigue and the basis for alertness management. Final report for the U.S. Department of Transportation, National Highway Traffic Safety Administration, DOT HS 808-762, pp. 1-113, 1998.

Mallis, M., Maislin, G., Konowal, N., Byrne, V., Bierman, D., Davis, R., Grace, R., Dinges, D.F.: *Biobehavioral responses to drowsy driving alarms and alerting stimuli. Final report.*. Sponsored by the National Highway Traffic Safety Administration, Office of Motor Carriers, 1999.

6. PRESENTATIONS AT SCIENTIFIC MEETINGS, CONFERENCES (N = 152)

Reviews of AFOSR PRET Center Progress by External Scientific Advisory Board.

July 31, 1995, Philadelphia, PA (hosted by University of Pennsylvania)
June 11, 1997, San Francisco, CA (hosted by Stanford University)
July 17, 1998, Boston, MA (hosted by Harvard University)

1995-2000 Presentations (total N = 152)

1995 chronological (n = 3)

DM Edgar: Symposium presentation "SCN-dependent alerting: A phenomenon generalizable from mouse to man?," a symposium presentation entitled "Does sleep homeostasis deteriorate with aging?," Workshop entitled "Behavioral State-related neurochemical sampling and drug delivery: What is state of the art?," and a poster presentation entitled "Wakefulness, motor activity, and compensatory sleep responses following caffeine, methamphetamine, and modafinil treatment in rats." World Federation of Sleep Research Societies, Nassau, The Bahamas, September 12-16, 1995.

DF Dinges: "Sleepiness, driving performance and implications." 1995 SAE International Truck and Bus Meeting and Exposition, US Department of Transportation, Federal Highway Administration, Winston-Salem NC, November 13, 1995.

DM Edgar: Poster presentation entitled "Low-dose treatment with the selective dopamine uptake blocker GBR-12909 increases wakefulness without intensifying motor activity in the rat" (Edgar, D.M., W.F. Seidel, W.C. Dement, and E. Mignot, Soc. Neuroscience Abst. 21: 180, 1995). Society for Neuroscience Annual Meeting, San Diego CA, November, 1995.

1996 chronological (n = 29)

D-J Dijk: "Role of the circadian pacemaker and sleep homeostasis in the regulation of sleep timing, sleep structure and the sleep EEG." Invited lecture for the International Workshop on Basic Sleep Regulating Mechanisms (AA Borbely, I Tobler, P Achermann; organizers), Monte Verita, Ascona, Switzerland, March 1996.

DF Dinges: "Sleep and health." Fourth International Congress of Behavioral Medicine, Washington DC, March 15, 1996.

DF Dinges: "New science on an old mystery: Sleep and its interactions with waking functions." National Science Teachers' Association, St. Louis MO, March 29, 1996.

DF Dinges: "Neurobehavioral effects of arousals." Fourth Meeting on Respiration and Sleep, Charlottesville VA, March 31, 1996.

DF Dinges: "Fatigue research and physiology." Flight Safety Foundation's 41st Annual Corporate Aviation Safety Seminar, Lake Buena Vista FL, April 25, 1996.

DF Dinges: "Napping strategies in fatigue management." Aerospace Medical Association, Atlanta GA, May 8, 1996.

DM Edgar: Scientific Program Committee, and symposium organizer, slide symposium presentation, and general symposium presentation entitled "Practical Circadian Biology in the Clinic and the Workplace." Society for Research on Biological Rhythms, Fifth Meeting, Amelia Island FL, May 8-12, 1996.

DF Dinges: "Sleepiness, its relationship to accidents, and the potential countermeasures." Fifth Meeting of the Society for Research on Biological Rhythms, Jacksonville FL, May 10, 1996.

DF Dinges: "Current research and future directions -- Overview." National Sleep Foundation's International Forum on Sleeplessness and Crashes '96, Washington DC, May 28, 1996.

DM Edgar: Course Organizer and Lecturer. "The Circadian Control of Sleep & Wakefulness: Basic Mechanisms & Clinical Perspectives. Association of Professional Sleep Societies 10th Annual Meeting, Washington DC, May 28, 1996.

D-J Dijk: "Spectral changes in sleep EEG activity in response to sleep loss." Invited lecture in the Symposium "100 years since Patrick and Gilbert: Advances in Science on the Neurobehavioral Effects of Human Sleep Deprivation." Association of Professional Sleep Societies 10th Annual Meeting, Washington DC, May 28-June 2, 1996.

DM Edgar: Participant, Slide Symposium, and Poster Presentation. "NonREM sleep in rats after various wake-promoting agents." Association of Professional Sleep Societies 10th Annual Meeting, Washington DC, May 28-June 2, 1996.

ME Jewett: Homeostatic and circadian components of subjective alertness interact in an non-additive manner. Oral presentation in the Original Investigations session: "Alertness and Performance" Association of Professional Sleep Societies 10th Annual Meeting, Washington DC, May 28-June 2, 1996.

DF Dinges: "Federal and private initiatives in the evaluation and management of sleepiness-related fatigue in transportation." Association of Professional Sleep Societies 10th Annual Meeting, Washington DC, May 29, 1996.

DF Dinges: "100 years since Patrick and Gilbert: Advances in science on the neurobehavioral effects of human sleep deprivation." Association of Professional Sleep Societies 10th Annual Meeting, Washington DC, May 30, 1996.

DF Dinges: "Biomedical basis of fatigue and loss of alertness in human operations." American Public Transit Association, Atlanta GA, June 3, 1996.

DF Dinges: "Physiological correlates of sleep deprivation." Third Clintec International Horizons Conference, Amsterdam, The Netherlands, June 9, 1996.

DF Dinges: "Effects of melatonin on human sleep and performance." 13th Congress of the European Sleep Research Society, Brussels, Belgium, June 16, 1996.

ME Jewett: Homeostatic and circadian components of subjective alertness interact in a non-additive manner during 48 hours of sleep deprivation. Invited presentation in the Young Scientists' Symposium of the 13th Congress of the European Sleep Research Society. Brussels, Belgium, June 16-21, 1996.

RE Kronauer: A model for reduced circadian modulation of alertness at extremes of homeostatic influence. Invited presentation in the symposium "Modeling of interactions between homeostatic and circadian processes". 13th Congress of the European Sleep Research Society. Brussels, Belgium, June 16-21, 1996.

DM Edgar: Symposium Presentation "The SCORE Sleep/Wake Bioassay for Drug Discovery and Evaluation." International Business Communications Conference on "Psychopharmacological Treatments for Sleep Disorders," San Francisco CA, July 18-19, 1996.

D-J Dijk: "Sleep and Polysomnography." 50th Anniversary Meeting, American Clinical Neurophysiology Society, Boston, MA, September 5, 1996.

DF Dinges: "Fatigue-reduction strategies for aviation, maritime, railway, and trucking operations." Flight Safety Foundation, Paris, France, September 17, 1996.

D-J Dijk: "Quantifying circadian and homeostatic aspects of sleep in forced desynchrony protocol." Providence, RI, September 20, 1996.

DF Dinges: "Work accidents and fatigue: An occupational health issue." 25th International Congress on Occupational Health, Stockholm, Sweden, September 20, 1996.

DF Dinges: "Sleep Loss: Effects of performance and countermeasures." American Petroleum Institute and U.S. Coast Guard, Washington, DC, October 8, 1996.

J Wyatt: "Modulation of Neurobehavioral Functions by Circadian- and Sleep/Wake Dependent Processes." Seminar, Endocrine Division, Brigham and Women's Hospital, Boston, MA, November 12, 1996.

DF Dinges: "Functional impact of sleep deprivation." Harvard Medical School, Brigham and Women's Hospital, Boston, MA, November 16, 1996.

D-J Dijk: "Quantifying the contribution of circadian and homeostatic processes to sleep propensity, sleep structure, alertness, and mood in healthy subjects." Seminar, NIMH, Psychobiology Branch, Bethesda, MD, 1996.

1997 chronological (n = 23)

CA Czeisler: "Aging, Sleep and Spaceflight." National Institute of Aging/NASA Workshop on Aging and Spaceflight, February 2-4, 1997.

DF Dinges: "Sleepiness: A Modern Hazard; Etiology and Assessment." Annual Cherry Blossom Conference, American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc., Arlington, VA, March 21, 1997.

DF Dinges: "Effects of Sleepiness on Society." Annual Cherry Blossom Conference, American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc., Arlington, VA, March 21, 1997.

J Mullington: "Sleep and the pineal." The French Institute for Culture and Technology of the University of Pennsylvania – *Anee Descartes*, Commemorative Celebration Lecture Series, Body and Mind: Consciousness and Unconsciousness, Philadelphia, PA, March 27, 1997.

DF Dinges: "The Effects of Sleep Duration and Cumulative Sleep Loss on Hypovigilance: Individual Sensitivity." 3rd International Meeting on Sleep Disorders, Bordeaux, France, April 17, 1997.

DF Dinges, JW Powell, and MM Mallis: "Countermeasures for jet lag and sleep deprivation." Basic Research in the National Defense, US House of Representatives, Washington D.C., May 7, 1997.

DF Dinges: "Jet Lag and Sleep Deprivation." Basic Research in the National Defense: University Contributions to Defense Readiness and Technology, Washington, DC, May 7, 1997.

DF Dinges: "Cumulative Effects of Fatigue on Performance: Operational Relevance." 68th Annual Scientific Meeting, Aerospace Medical Association, Chicago, IL, May 15, 1997.

DF Dinges: "Neurobehavioral and neuroimmune effects of severe total sleep deprivation." 9th Annual Convention, American Psychological Society, Washington, DC, May 23, 1997.

CA Czeisler: "Sleep-wake regulation and circadian rhythms." Scientific Keynote Address, 11th Annual Meeting, Association of Professional Sleep Societies, San Francisco, CA, June 12, 1997.

J Wyatt: "Consciousness and Sleep: Awareness, Attention, and Memory During Sleep." 11th Annual Meeting, Association of Professional Sleep Societies, San Francisco, CA, June 12, 1997.

MJH Kas: "Sleep-Wake architecture in a diurnal rodent, Octadon degus." Poster Symposium, 11th Annual Meeting, Association of Professional Sleep Societies, San Francisco, CA, June 12-15, 1997.

WF Seidel: "NonREM sleep recovery in rats: Comparison of dopamine uptake inhibitors with other wake-promoting agents." Poster Symposium, 11th Annual Meeting, Association of Professional Sleep Societies, San Francisco, CA, June 12-15, 1997.

SW Wurts: "Effects of suprachiasmatic nucleus lesions on REM sleep continuity." Poster Symposium, 11th Annual Meeting, Association of Professional Sleep Societies, San Francisco, CA, June 12-15, 1997.

J Wyatt: "Interaction of Circadian- and Sleep/Wake Homeostatic-Processes Modulate Psychomotor Vigilance Test (PVT) Performance." 11th Annual Meeting, Association of Professional Sleep Societies, San Francisco, CA, June 13, 1997.

D-J Dijk: "Experimental Manipulation of Circadian Desynchronization." Symposium: Circadian Desynchronization-Theoretical and Practical Implications, 11th Annual Meeting, Association of Professional Sleep Societies, San Francisco, CA, June 14, 1997.

J Wyatt: "Circadian- and Sleep/Wake Homeostatic-Modulation of Neurobehavioral Factors: The Forced Desynchrony Protocol." Seminar, Chronobiology/Sleep Research Laboratory, EP Bradley Hospital, Providence, RI, June 25, 1997.

D-J Dijk: "Light, circadian rhythms and sleep." Presentation: Sleep Beyond Sleep Apnoea, Summer Meeting of the British Thoracic Society, Loughborough, United Kingdom, July 4, 1997.

DM Edgar: "Circadian and homeostatic control of sleep-wakefulness: Relevance in the treatment of sleep disorders." Sleep Disorders Medicine Silver Anniversary Symposium, Treatment Strategies for

Sleep/Wakefulness Disorders in Jet-Lag and Shift-Work, Stanford University School of Medicine, Stanford, CA, July 18, 1997.

DF Dinges: "Homeostatic and circadian regulation of wakefulness during jet lag and sleep deprivation: Effect of wake-promoting countermeasures on the development of neurobehavioral deficits." AFOSR Chronobiology and Neural Adaptation Program Review, US Air Force Academy, Colorado Springs, CO, September 18-20, 1997.

DM Edgar: "Pre-clinical assessment of compensatory sleep responses to drug-induced waking." AFOSR Chronobiology and Neural Adaptation Program Review, US Air Force Academy, Colorado Springs, CO, September 18-20, 1997.

DF Dinges: "New technology in vigilance monitoring." 3rd Annual Conference on Highway Accident Litigation, American Trucking Associations Litigation Center, Monterey, CA, September 22, 1997.

DF Dinges: "Fatigue, desynchronosis and countermeasures." Aerospace Medicine Lecture, Alliance of Air National Guard Flight Surgeons, Nashville, TN, November 16, 1997.

1998 chronological (n = 29)

DF Dinges: "Managing fatigue by drowsiness detection: Can technological promises be realized?" 3rd International Conference on Fatigue in Transportation, Main Roads Western Australia, Fremantle, Western Australia, February 10, 1998.

DM Edgar: "Dopaminergic mechanisms in sleep homeostasis." ARO Workshop: New Directions in Understanding Sleep Need and Human Vulnerability to Sleep Loss, April 3, 1998.

DJ Dijk: "Interaction between sleep and circadian rhythms." Society for Research on Biological Rhythms Workshop, Amelia Island, FL, May, 1998.

DM Edgar: "Interaction between sleep and circadian rhythms." Society for Research on Biological Rhythms Workshop Presentation, Amelia Island, FL, May, 1998.

MM Mallis: "Technological solutions to fatigue management: A controlled double–blind validation trial on six technologies." Annual Scientific Meeting of the Aerospace Medical Association (ASMA), Seattle, WA, May 19, 1998.

CA Czeisler: "Circadian control of performance: Coping with night work and jet lag." AFOSR Night Operations and Circadian Rhythms Workshop, Charleston AFB, Charleston, NC, May 29, 1998.

DF Dinges: "Performance effects cumulative sleep loss: What are the countermeasures?" AFOSR Night Operations and Circadian Rhythms Workshop, Charleston AFB, Charleston, NC, May 29, 1998.

DM Edgar: "Pharmacology of wake-promoting somnolytic agents." AFOSR Night Operations and Circadian Rhythms Workshop, Charleston AFB, Charleston, NC, May 29, 1998.

DJ Dijk: "Circadian and homeostatic determinants of the EEG during wakefulness: Implications for EEG monitoring of vigilance." 12th Annual Meeting of the Association of Professional Sleep Societies (APSS) Symposium, New Orleans, LA, June, 1998.

DJ Dijk: "Is REM sleep regulated by waking or by nonREM sleep." 12th Annual Meeting of the Association of Professional Sleep Societies (APSS) Workshop, New Orleans, LA, June, 1998.

DM Edgar: "Opponent processes in sleep-wake regulation: Potential role for dopamine." 12th Annual Meeting of the Association of Professional Sleep Societies (APSS) Symposium (Hypothalamic Mechanisms of Sleep and Arousal Regulation), New Orleans, LA, June, 20, 1998.

MM Mallis: "New drowsiness detection technologies: Testing their validity to track hypovigilance." 12th Annual Meeting of the Association of Professional Sleep Societies (APSS), New Orleans, LA, June 21, 1998.

DM Edgar: "Interaction between sleep and circadian rhythms: SCN and sleep regulation." FASEB Summer Conference on Neurobiology of Vertebrate Circadian Rhythm Entrainment, July 13, 1998.

MM Mallis: "Vigilance performance validation of new technologies for fatigue monitoring." Third Annual Review of Air Force Office of Scientific Research Partnership for Research Excellence Transition (AFOSR PRET) Center, Countermeasures for Jet Lag and Sleep Deprivation, Harvard University, MA, July 17, 1998.

DF Dinges: "Sleep imperative in maintaining performance and safety in a 24-hour society." American Psychological Association, San Francisco, California, August 16, 1998.

DF Dinges: "The new applied science of fatigue countermeasures." ATA Litigation Center Conference on Highway Accident Litigation, Scottsdale, Arizona, September 14, 1998.

ME Jewett: "Mathematical models of human performance and alertness." Invited presentation for the Providence Sleep Research Group, Brown University, Providence, Rhode Island, September, 1998.

DM Edgar: "The Circadian and Homeostatic Control of Wakefulness and Sleep." Michigan State University Program in Neuroscience, Michigan, September 24, 1998.

DF Dinges: "Physiology of human sleep and fatigue and potential countermeasures for adoption in the transit industry." Annual APT Meeting, New York City, New York, October 7, 1998.

DM Edgar: "Practical Approaches to Shift-Work and Other Insomnias." Sleep for A to Zzz, Summit Medical Center, Oakland, California October 21, 1998.

DF Dinges: "Sleep disorders: Insomnia, daytime sleepiness and fatigue." CME course, Harvard University, Boston, Massachusetts, October 23, 1998.

DF Dinges: NBAA Workshop, Las Vegas, Nevada, October 27, 1998.

DM Edgar: "Wakefulness-Promoting Therapeutics and Sleep Homeostasis," Grand Rounds, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, October 29, 1998.

DF Dinges: "How much sleep we need depends on how we define wakefulness." Swedish Sleep Research Society, Stockholm, Sweden, November 23, 1998.

DF Dinges: "Sleep need: New neurobehavioral science on an old mystery." Swedish Physicians Society, Gothenburg, Sweden, November 25, 1998.

CA Czeisler: Keynote Speaker NSF Center for Biological Timing and National Center for Sleep Disorders Research, NIH. Workshop on "What is sleep? What is it good for?" jointly sponsored by the National Center on Sleep Disorders Research, National Heart, Lung, and Blood Institute, National Institute of Mental Health, National Institute on Aging, and the National Science Foundation Center for Biological Timing, Dulles, Virginia, November/December, 1998.

DM Edgar: Workshop on "What is Sleep? What is it Good For?" jointly sponsored by the National Center on Sleep Disorders Research, National Heart, Lung, and Blood Institute, National Institute of Mental Health, National Institute on Aging, and the National Science Foundation Center for Biological Timing, Dulles, Virginia, November/December, 1998.

DF Dinges: "Sleep need and neurobehavioral vulnerability to sleep loss." Workshop on "What is sleep? What is it good for?" jointly sponsored by the National Center on Sleep Disorders Research, National Heart, Lung, and Blood Institute, National Institute of Mental Health, National Institute on Aging, and the National Science Foundation Center for Biological Timing, Dulles, Virginia, November/December, 1998.

DF Dinges: "Neurobehavioral determinants and consequences of sleepiness in a world that values wakefulness." Medical Grand Rounds, Yale School of Medicine, New Haven, Connecticut, December 16, 1998.

1999 chronological (n = 49)

CA Czeisler: "Ambient light intensity, actigraphy, sleep and respiration, circadian temperature and melatonin rhythms and daytime performance of crew members during space flight on STS90 and STS-95 missions." First Biennial Space Biomedical Investigators Workshop, League City, Texas, January 11-13, 1999.

D-J Dijk: "Electroencephalographic and Ocular Correlates of Neurobehavioral Performance Decrements." First Biennial Space Biomedical Investigators Workshop, League City, Texas, January 11-13, 1999.

HPA VanDongen: "Circadian and homeostatic interactions in waking neurobehavioral functions during partial and total sleep deprivation: Effects of caffeine." CMNR Workshop on Caffeine in Military Operations, Washington, DC, February, 1999.

DF Dinges: "Sleepiness and its impact on society." University of Pennsylvania School of Medicine CME course, Orlando, Florida, February 12, 1999.

DM Edgar: "Sleep and the Dopamine Transporter." National Institute on Drug Abuse, Molecular Neurobiology Branch, Baltimore, Maryland, February 24, 1999.

DM Edgar: "Dopamine and Sleep Homeostasis." University of Pennsylvania Medical Center, Center for Sleep and Respiratory Neurobiology, Philadelphia, Pennsylvania, February 26, 1999.

DM Edgar "Wake Promoting Therapeutics and Sleep Homeostasis." Keynote Address, 13th Annual Northeast Sleep Society Meeting, Princeton Medical Center, Princeton, New Jersey, March 19, 1999.

DF Dinges: "Shiftwork and performance." The Regional center for Sleep Disorders, Sunrise Hospital and Medical Center, Las Vegas, Nevada, March 30, 1999.

D-J Dijk: "Melatonin as a hypnotic for Neurolab crew." Presentation Neurolab Scientific Results Symposium, Washington, DC, April, 1999.

ME Jewett: "Homeostatic and circadian regulation of neurobehavioral function." Invited speaker for the Endocrine Research Conference, Endocrine-Hypertension Division, Brigham and Women's Hospital, Boston, Massachusetts, April, 1999.

DM Edgar: "Determinants of Sleepiness and Alertness," Grand Rounds, San Mateo Health Services Agency, April 13, 1999.

HPA Van Dongen: "Caffeine as a performance enhancing drug in Air Force Operations," Aerospace Medical Association Annual Scientific Meeting, Detroit, Michigan, May 16-20, 1999.

D-J Dijk: "Models of Human Sleep Regulation." Invited Participant & Co-Chair, Workshop on Biomathematical Models of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans, MIT Endicott House, Dedham, Massachusetts, May 18-21, 1999.

DM Edgar: "Integration of Models." Invited Discussant, Workshop on Biomathematical Models of Circadian Rhythmicity, Sleep Regulation, and Neurobehavioral Function in Humans, MIT Endicott House, Dedham, Massachusetts, May 18-21, 1999.

DF Dinges: "Model of Human Neurobehavioral Function." Co-Chair, Workshop on Biomathematical Models of Circadian Rhythmicity, Sleep Regulation, and Neurobehavioral Function in Humans, MIT Endicott House, Dedham, Massachusetts, May 18-21, 1999.

ME Jewett: "Quantifying human circadian pacemaker response to brief, extended and repeated light episodes over the photopic range." Invited speaker, Workshop on Biomathematical Models Of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans, MIT Endicott House, Dedham, Massachusetts, May 18-21, 1999.

ME Jewett: "Interactive mathematical models of subjective alertness and cognitive throughput in humans." Invited Speaker, Workshop on Biomathematical Models Of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans, MIT Endicott House, Dedham, Massachusetts, May 18-21, 1999.

ME Jewett: "Comparison of model predictions of experimental protocols." Invited Speaker, Workshop on Biomathematical Models Of Circadian Rhythmicity, Sleep Regulation and Neurobehavioral Function in Humans, MIT Endicott House, Dedham, Massachusetts, May 18-21, 1999.

DF Dinges: "Chronic sleep deprivation: Mechanisms and consequences." Fourth International Meeting on Sleep Disorders, Sommeil: De La Naissance a la Mort Conference, Bordeaux, France, May 27, 1999.

D-J Dijk: "Human sleep-wake regulation, aging and the electroencephalogram: A circadian perspective." Invited presentation for the Workshop The Regulation of Sleep; Human Frontier Science Program, Strasbourg, France, June, 1999.

D-J Dijk: "Sleep in space: a circadian perspective." Invited presentation 20th Annual International Gravitational Physiology Meeting, Orlando, Florida, June, 1999.

DM Edgar: Invited Plenary Lecture, "Non-Photic Entrainment of the Circadian Timing System," 1999 Dutch Neuro-Endo Meeting, Doowerth, The Netherlands, June 3, 1999.

DF Dinges: "Neurobehavioral effects of sleep loss: Homeostatic and circadian dynamics." Gordon Conference, Chronobiology Section, Barga, Italy, June 17, 1999.

D-J Dijk: "Sleep and circadian rhythms in astronauts on Neurolab." Invited presentation for the symposium Astronauts/cosmonauts: Sleep and Rhythms. 13th Annual Meeting of the Association of Professional Sleep Societies, Orlando, Florida, June, 1999.

DF Dinges: "Accident-prevention with technologies: Fatigue-management and drowsiness detection." 13th Annual Meeting of the Association of Professional Sleep Societies, Orlando, Florida, June 20, 1999.

DF Dinges: "Chronic sleep restriction: Neurobehavioral effects of 4-hour, 6-hour, and 8-hour TIB." 13th Annual Meeting of the Association of Professional Sleep Societies, Orlando, Florida, June 22, 1999.

DF Dinges: "New technologies for monitoring drowsy driving: Scientific, practical, and legal issues." 13th Annual Meeting of the Association of Professional Sleep Societies, Meet the Professor Luncheon, Orlando, Florida, June 23, 1999.

DM Edgar: "Opponent Process View of SCN Regulation of Arousal." Invited Symposium Lecture, New insights into neural circuitry underlying circadian regulation of sleep and waking (Dr. G. Aston-Jones, organizer), 13th Annual Meeting of the Association of Professional Sleep Societies, Orlando, Florida, June 24, 1999.

DF Dinges: "Causes of, and contributing factors to fatigue." House of Representatives Standing Committee on Communications, Transport and the Arts, Melbourne, Australia, July 27, 1999.

DF Dinges: "Key actions to reduce fatigue related accidents on the road and in the workplace – lessons we can learn from the aviation and military experience." Transportation Seminar, Melbourne, Australia, July 28, 1999.

DF Dinges: "Napping Strategies." Transportation Seminar, Melbourne, Australia, July 28, 1999.

DF Dinges: "Neurobehavioral consequences to sleepiness: What if anything accumulates with sleep debt?" Australasian Sleep Association 1999 Annual Scientific Meeting, Coolangatta, Australia, July 30, 1999.

DF Dinges: "Sleepiness and Fatigue – the Catastrophic Consequences." Australasian Sleep Association 1999 Annual Scientific Meeting, Coolangatta, Australia, July 31, 1999.

DF Dinges: "Behavioral risks of untreated sleep apnea." Australasian Sleep Association 1999 Annual Scientific Meeting, Coolangatta, Australia, August 1, 1999.

DF Dinges: "Sleep disorders and fatigue in industry." Australian Parliament Commission on Transportation, Sydney, August 3, 1999.

DF Dinges: "Human sleep deprivation: Lessons from the laboratory." Psychology Colloquium, University of New South Wales, Kensington, Australia, August 4, 1999.

DF Dinges: "Sleep loss and immune responses." National Institute of Health Sleep and Host Defense Mechanisms Meeting, Bethesda, Maryland, August 25, 1999.

DF Dinges: "What is wakefulness? Sleep need and circadian control of neurobehavioral functions." Keynote address at the International Congress on Chronobiology, Washington, DC, August 29, 1999.

DF Dinges: "Causes and solutions to fatigue in transportation." Keynote speaker at the National Congress and Transportation Expo, Melbourne, Australia, September 9, 1999.

DM Edgar: "Circadian and Homeostatic Control of Sleep-Wakefulness: Monoaminergic Interactions." University of Groningen, Groningen, The Netherlands, October 4, 1999.

DF Dinges: "Driver sleepiness: Validation and implementation of drowsy driving monitoring." Third International Congress on The Function and Functional Significance of Sleep, World Federation of Sleep Research Societies, Dresden, Germany, October 7, 1999.

DF Dinges: "Educating government and federally regulated industries about sleep." Third International Congress on The Function and Functional Significance of Sleep, World Federation of Sleep Research Societies, Dresden, Germany, October 7, 1999.

DF Dinges: "Human immune status during prolonged sleep deprivation, circadian rhythmicity, sleep drive, stress and caffeine." Third International Congress on The Function and Functional Significance of Sleep, World Federation of Sleep Research Societies, Dresden, Germany, October 7, 1999.

HPA VanDongen: "Sleep inertia following 2-hour naps occurring every 12 hours during 88 hours of partial sleep deprivation." Congress Focus Group on Neuropsychology of Sleep and Awakening, World Federation of Sleep Research Societies, Dresden, Germany, October 7, 1999.

DM Edgar: Invited Symposium Lecture, "Evidence for Interaction Between Sleep and Circadian Systems in Animals" In: Determinants of Vigilance: Interaction Between the Sleep and Circadian Systems (Dr. A. Pack, organizer), American Physiological Society, Ft. Lauderdale, Florida, October 19-22, 1999.

DF Dinges: "Behavioral consequences and the interaction between circadian and sleep systems." In: Determinants of Vigilance: Interaction Between the Sleep and Circadian Systems (Dr. A. Pack, organizer), American Physiological Society, Ft. Lauderdale, Florida, October 21, 1999.

DF Dinges: "Detecting drowsiness and fatigue: Lessons from the laboratory." Drexel University School of Biomedical Engineering, Science and Health Systems, Philadelphia, Pennsylvania, November 5, 1999.

DF Dinges: "Chronic sleep debt and the quality of wakefulness." Belgian Association for the Study of Sleep, Autumn International Meeting, Brussels, Belgium, November 20, 1999.

DF Dinges: "Sleep need and neurobehavioral function: Can we adapt to sleep loss?" Sleep Grand Rounds, Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts, December 8, 1999.

2000 chronological (n = 19)

DM Edgar: "Stimulant Interaction with Sleep Homeostasis." Walter Reed Army Institute of Research, Washington, DC, February 8, 2000.

DF Dinges: "Sleep loss: From moods to mars." Grand Rounds at the University of Pennsylvania Health System Department of Psychiatry, Philadelphia, Pennsylvania, February 24, 2000.

DF Dinges: "Sleep deprivation-induced cytokine disturbances." 56th Annual Meeting of the American Academy of Allergy, Asthma and Immunology, San Diego, California, March 6, 2000.

DF Dinges: "Human performance in the 21st century: A sea of troubles." Maritime Human Factors 2000 Conference, Maritime Institute, Linthicum, Maryland, March 13, 2000.

DF Dinges: "Stress, fatigue and behavioral energy." In: Defining Energy for a New Millenium, International Life Sciences Institute of North America Meeting, Project Committee on Energy, Washington, DC, April 5, 2000.

DF Dinges: "Sleep, sleep deprivation and affect." In: The Neurobiology of Positive Emotion, Six Annual Wisconsin Symposium on Emotion, Health Emotions Research Institute, University of Wisconsin, Madison, Wisconsin, April 14, 2000.

DF Dinges: "Where do we go from here?" Second Annual Southern Alleghenies Regional Sleep Conference, Altoona, Pennsylvania, April 27, 2000.

ME Jewett: "Are circadian models medically useful?" Invited presentation for the symposium Construction of Circadian Models. Society for Research on Biological Rhythms Meeting, Amelia Island, Florida, May, 2000.

NL Rogers: "Effect of repeated caffeine administration on core body temperature during 88 hours of sustained wakefulness." Society for Research on Biological Rhythms Meeting, Amelia Island, Florida, May, 2000.

DF Dinges: "Accidents and fatigue – road/air/sea." Sleep, Sleepiness, Sleep Apnea and Driving Symposium, Stockholm, Sweden, May 26, 2000.

DF Dinges: "Alertness Monitors." Sleep, Sleepiness, Sleep Apnea and Driving Symposium, Stockholm, Sweden, May 26, 2000.

ME Jewett: "Circadian pacemakers as limit cycle oscillators." Presentation for Biomathematical Modeling Summer Program. Harvard Medical School, Boston, Massachusetts, June, 2000.

DF Dinges: "Dose-response effects of chronic sleep restriction on sleep and waking functions: Results from randomized controlled trials." 14th Annual Meeting of the Association of Professional Sleep Societies, Las Vegas, Nevada, June 20, 2000.

DF Dinges: "Field measurement of EDS." 14th Annual Meeting of the Association of Professional Sleep Societies, Las Vegas, Nevada, June 20, 2000.

DF Dinges: "Neurobehavioral effects of 66 hours of sustained low-dose caffeine during 88 hour of total sleep deprivation." 14th Annual Meeting of the Association of Professional Sleep Societies, Las Vegas, Nevada, June 20, 2000.

DF Dinges: "New understanding in sleepiness and neurobehavioral performance." 14th Annual Meeting of the Association of Professional Sleep Societies, Las Vegas, Nevada, June 20, 2000.

HPA VanDongen: "Sustained low-dose caffeine administration reduces sleep inertia after nap sleep during 88h extended wakefulness." 14th Annual Meeting of the Association of Professional Sleep Societies, Las Vegas, Nevada, June, 2000.

ME Jewett: "Challenges involved in practical application of neurobehavioral models." Presentation for Circadian Scientific Meeting, Harvard Medical School, Boston, Massachusetts, July, 2000.

7. CONSULTATIVE / ADVISORY TO OTHER LABORATORIES/AGENCIES (N = 42)

1995-2000 chronological (Total N = 42)

1. DM Edgar, Stanford University
   Institution: Air Force military staging areas in northern Alaska
   Activity: Collaboration in ongoing study of sleep-wakefulness in Alaskan Black Bears. Animals obtained from Air Force military staging areas in northern Alaska.
   Location: University of Alaska, Fairbanks, Alaska
   Dates: May 1995-present

2. DF Dinges, University of Pennsylvania
   Institution: AFOSR/NL, 11 Air Force personnel, 3 other academic consultants
   Activity: Advisor at the Air Force Office of Scientific Research Night Operations and Human Chronobiology Workshop, Stealth Squadrons.
   Location: Holloman AFB, NM
   Dates: January 4-5, 1996

3. DF Dinges, University of Pennsylvania
   KA Gillen, University of Pennsylvania
   EC Orne, University of Pennsylvania
   CA Czeisler, Brigham and Women's Hospital / Harvard Medical School
   DJ Dijk, Brigham and Women's Hospital / Harvard Medical School
   JK Wyatt, Brigham and Women's Hospital / Harvard Medical School
   ME Jewett, Brigham and Women's Hospital / Harvard Medical School
   JM Ronda, Brigham and Women's Hospital / Harvard Medical School
   R Kronauer, Harvard University
   E Yates, Alza Corporation
   Institution: Alza Corporation
   Activity: Consultation to standardize neurobehavioral and physiological protocols at University of Pennsylvania and the Brigham and Women's Hospital. Advisory discussion with Alza representative on use of caffeine.
   Location: Brigham and Women's Hospital / Harvard, Boston, MA
   Dates: February 14, 1996.

4. DF Dinges, University of Pennsylvania
   KA Gillen, University of Pennsylvania
   EC Orne, University of Pennsylvania
   CA Czeisler, Brigham and Women's Hospital / Harvard Medical School
   DJ Dijk, Brigham and Women's Hospital / Harvard Medical School
   JK Wyatt, Brigham and Women's Hospital / Harvard Medical School
   ME Jewett, Brigham and Women's Hospital / Harvard Medical School
   JM Ronda, Brigham and Women's Hospital / Harvard Medical School
   R Kronauer, Harvard University
   S Koretz, Alza Corporation
   E Yates, Alza Corporation

TL Baker, Shiftwork Systems
Institution: Alza Corporation, Shiftwork Systems
Activity: Meeting of PRET investigators and industry partners to discuss transition of PRET products and developmental issues.
Location: Brigham and Women's Hospital / Harvard, Boston, MA
Dates: April 3, 1996

5. DF Dinges, University of Pennsylvania
D-J Dijk, Brigham and Women's Hospital / Harvard Medical School
T Åkerstedt, Karolinska Institute
MR Rosekind, NASA Ames Research Center
G Haddad, AFOSR/NL
A Gevins, SAM Technology, Inc.
Institution: SAM Technology, Inc.
Activity: Advisory discussion of how to utilize state-of-the-art EEG technologies for fatigue detection. New collaboration initiatives explored.
Location: SAM Technology, Inc., San Francisco, CA
Dates: July 31, 1996

6. DM Edgar, Stanford University
DF Dinges, University of Pennsylvania
Institution: Brown University
Activity: Advisor to Dr. Mary Carskadon and Dr. Barbara Tate, Sleep studies in the *Octadon degus*.
Location: Stanford University, Palo Alto, CA
Dates: July 31 - August 2, 1996.

7. DF Dinges, University of Pennsylvania
CA Czeisler, Brigham and Women's Hospital / Harvard Medical School
MR Rosekind, NASA Ames Research Center
G Haddad, AFOSR/NL
RC Graeber, Boeing Commerical Airplane Group
14 other Boeing employees
Institution: Boeing Commerical Airplane Group
Activity: Demonstration of new automated glass cockpits; presentation on PRET Center activity; advisory discussion of implications of PRET Center initiatives and findings in airplane design.
Location: Boeing Commercial Airplane Group, Seattle, WA
Date: August 1, 1996

8. DM Edgar, Stanford
Institutions: Cephalon, Inc.
Co-Censys, Inc.
Glaxo SpA
Gliatech, Inc.
Neurogen, Inc.
Smith-Kline Beecham Pharmaceuticals, UK
Activity: Consultation and collaboration towards pre-clinical drug discovery of novel sleep-wake therapeutics and circadian rhythm phase-shifting medications.
Location: Stanford University, Stanford, CA
Date: August , 1996-August, 1997

9. DF Dinges, University of Pennsylvania
   Institution: Cephalon (Lynne Brooks)
   Activity: Expert advice on performance impairment from sleepiness.
   Location: University of Pennsylvania, Philadelphia, PA
   Dates: October 24, 1996

10. DF Dinges, University of Pennsylvania
   Institution: Wyeth-Ayerst
   Activity: Expert advice on performance impairment from dyssomnia and on sleep facilitation.
   Location: University of Pennsylvania, Philadelphia, PA
   Dates: November 5, 1996; August 19, 1997

11. DF Dinges, University of Pennsylvania
   Institution: NASA-Ames Research Center
   Activity: Countermeasures to performance impairment from fatigue: Study design and assessment.
   Location: Moffett Field, CA
   Dates: January 5-8, 1997
   June 9, 1997
   July 29-August 1, 1997

12. DF Dinges, University of Pennsylvania
   Institution: NASA-Johnson Space Center
   Activity: Selection of scientific and technical hardware for life science research on the International Space Station.
   Location: Houston, TX
   Dates: July 27-28, 1997

13. DM Edgar, Stanford University
   Institutions: Army Research Office and Stanford University
   Activity: Collaboration in support of studies investigating neurotrophin regulation during sleep deprivation (research sponsored by ARO, T. Kilduff, PI). Studies required use of the SCORE Sleep-Wake Bioassay Facility (Dr. Edgar's laboratory) and the expertise of Dr. Edgar and his technical staff.
   Location: Stanford University, Stanford, CA
   Dates: August 1997-present

14. DF Dinges, University of Pennsylvania
   Institution: U.S. Department of Transportation (NHTSA, FHWA)
   Activity: Numerous consultations on standards for technologies to monitor drowsiness and fatigue during performance.
   Location: Washington, DC
   Dates: August, 1997 through August, 1999

15. DF Dinges, University of Pennsylvania
   Institution: Boeing Commercial Airplane Group, Human Factors Division
   Activity: Expert advice on incorporation of fatigue tracking technologies in the cockpit.
   Location: Seattle, WA
   Dates: May 20, 1998

16. DF Dinges, University of Pennsylvania
Institution: NASA Ames Research Center
Activity: Consultation on development of a Boeing 747-400 simulator study evaluating alertness of pilots during a night flight after prolonged wakefulness.
Location: Moffett Field, CA
Dates: May 21, 1998

17. DF Dinges, University of Pennsylvania
Institution: NASA Ames Research Center
Activity: Consultation on statistical analyses to be performed on "Alertness During a Night Flight After Prolonged Wakefulness: A Simulator Study."
Location: Moffett Field, CA
Dates: August 17, 1998

18. DF Dinges, University of Pennsylvania
Institution: Massachusetts Institute of Technology (NSBRI External Advisory Council)
Activity: To review sleep deprivation effects on immune function.
Location: Cambridge, MA
Dates: September 3-4, 1998

19. DF Dinges, University of Pennsylvania
Institution: NASA Johnson Space Center
Activity: Discussion on fatigue, sleep and sleep assessment.
Location: Houston, TX
Dates: October 8, 1998

20. DF Dinges, University of Pennsylvania
Institution: NASA Johnson Space Center (Dr. Chris Flynn)
Activity: Advising flight surgeons on the measurement of fatigue and performance impairment in astronauts.
Location: Houston, TX
Dates: November, 1998

21. DF Dinges, University of Pennsylvania
Institution: Carnegie Mellon Research Institute (CMRI)
Activity: To review results from objective fatigue monitor on driver performance.
Location: Pittsburgh, PA
Dates: November 4, 1998

22. DF Dinges, University of Pennsylvania
Institution: NASA Johnson Space Center
Activity: Review of performance impairment in relation to sleep and circadian biology: The development of countermeasures.
Location: Houston, TX
Dates: January 10-14, 1999

23. DF Dinges, University of Pennsylvania
Institution: NASA Ames Research Center
Activity: Planning and implementation of a Boeing 747-400 simulator study on objective monitors of

vigilance.
Location: Moffet Field, CA
Dates: February 6-8, 1999

24. DF Dinges, University of Pennsylvania
Institution: Boeing Commercial Airplane Group, Human Factors Division
Activity: Expert advice on incorporation of fatigue tracking technologies in the cockpit.
Location: Seattle, WA
Dates: February 9, 1999

25. DF Dinges, University of Pennsylvania
Institution: Johnson Hopkins University Applied Physics Lab
(NSBRI External Advisory Council)
Activity: To review sleep deprivation effects on immune function.
Location: Baltimore, MD
Dates: February 22-23, 1999

26. DF Dinges, University of Pennsylvania
Institution: Johns Hopkins University Applied Physics Lab
Activity: Discussion on development of automated blood acquisition system.
Location: Baltimore, MD
Dates: April 23, 1999

27. DF Dinges, University of Pennsylvania
Institution: U.S. Department of Transportation (FHWA)
Activity: Discussion on development of objective, ocular-based measures of vigilance.
Location: Herndon, VA
Dates: April 26, 1999

28. DF Dinges, University of Pennsylvania
Institution: NASA Ames Research Center (Dr. David Neri)
Activity: Implementation of a Boeing 747-400 simulator study on objective monitors of vigilance.
Location: Moffet Field, CA
Dates: May 7, 1999

29. DF Dinges, University of Pennsylvania
Institution: U.S. Department of Transportation (NHTSA)
Activity: Review continuing validation and implementation of PERCLOS as an objective vigilance detection system.
Location: Moffet Field, CA
Dates: May 13, 1999

30. ME Jewett, Harvard University
Institution: Psychiatrische Universitätsklinik (Dr. Anna Wirz-Justice)
Activity: Consult on circadian phase and amplitude assessment in patients with seasonal affective disorder.
Location: Harvard University, Boston, MA
Dates: June 1999-present

31. DF Dinges, University of Pennsylvania

Institution: NASA Johnson Space Center (Dr. Chris Flynn)
Activity: Discussion on development of tool for fatigue assessment in astronauts.
Location: Houston, TX
Dates: July 22, 1999

32. DF Dinges, University of Pennsylvania
Institution: National Institutes of Health (Dr. Michael Twery)
Activity: Workshop on sleep and host defense.
Location: Washington, DC
Dates: August 24-26, 1999

33. DF Dinges, University of Pennsylvania
Institution: National Transportation Safety Board (Mr. James Hall)
Activity: Testimony to NTSB on technologies for fatigue detection.
Location: Nashville, TN
Dates: August 31, 1999

34. DM Edgar, Stanford University
Institution: National Space Biomedical Research Institute (NSBRI)
Activity: Service on Research Funding Announcement Development Group responsible for establishing NSBRI research objectives in the area of sleep and circadian rhythms.
Location: Houston, TX
Dates: October 25-26, 1999

35. CA Czeisler, Harvard University
Rod Hughes, Harvard University
DF Dinges, University of Pennsylvania
Institution: Cephalon, Inc. (Dr. Frank Baldino)
Activity: Discussion of studies needed on modafinil as a countermeasure to jet lag and sleep deprivation.
Location: Boston, MA
Dates: January 5, 2000

36. DF Dinges, University of Pennsylvania
Institution: Brookhaven National Laboratory (Dr. Nora Volkow)
Activity: Discussion of experimental plan for neuroimaging GABA receptors in sleep deprived subjects.
Location: Brookhaven National Laboratory, NY
Dates: February 9, 2000

37. DF Dinges, University of Pennsylvania
Institution: MacArthur Foundation (Dr. Robert Rose)
Activity: Mechanisms of the placebo response.
Location: Naples, FL
Dates: February 17-18, 2000

38. ME Jewett, Harvard University
Institution: NASA Johnson Space Center (Dr. Chris Flynn)
Activity: Discussion on fatigue and the use of mathematical models to determine appropriate timing of countermeasures.
Location: Houston, TX

Dates: March 3, 2000

39. DF Dinges, University of Pennsylvania
Institution: NASA Ames Research Center (Dr. David Neri)
Activity: Review of research on fatigue management on the flight deck.
Location: Moffet Field, CA
Dates: March 7, 2000

40. ME Jewett, Harvard University
Institution: Boston University (Dr. John Howland)
Activity: Consultant on protocol design and use of PVT in studies of the effects of alcohol and sleep deprivation on performance in naval simulators.
Location: Harvard University, Boston, MA
Dates: May 2000-present

41. DF Dinges, University of Pennsylvania
Institution: Walter Reed Army Institute of Research
Activity: Review of WRAIR, USARIEM, and USAARL research programs on fatigue management and countermeasures.
Location: Silver Spring, MA
Dates: April 3, 2000

42. ME Jewett, Harvard University
Institution: Stanford University (Dr. Norman Ruby)
Activity: Consultant on limit cycle models and their application to circadian systems of Siberian Hamsters.
Location: Harvard University, Boston, MA
Dates: May 2000-present

Note: PRET Center investigators and industry partners also had a number of advisory and consultative communications via e-mail, telephone, fax, and in writing, as well as meetings specifically focused on methodological and technical aspects of the projects.

8. TRANSITIONS (N = 36)

1995-2000 Total N = 36

Provider: DF Dinges, CA Czeisler et al.
Recipient: Air Force Command Flight Surgeons and flight crews at Bolling AFB, Washington, DC
Result: Advisors at the Air Force Office of Scientific Research Night Operations / Human Chronobiology Workshop.
Application: Use of fatigue countermeasures in Air Force operations and deployment.

Provider: DF Dinges et al.
Recipient: Air Force Command Flight Surgeons and flight crews at Holloman Air Force Base, New Mexico
Result: Advisor at the Air Force Office of Scientific Research Night Operations and Human Chronobiology Workshop for F117 Stealth Squadrons.
Application: Use of fatigue countermeasures in Air Force night operations and deployment.

Provider: DF Dinges et al.

Recipient: Lt. Colonel Lex Brown, Holloman Air Force Base, New Mexico
Result: Comparison of sleep need versus sleep duration of F117, F4, and HH60 pilots.
Application: Development of scheduling techniques.

Provider: DF Dinges et al.
Recipient: Lt. Colonel George Talley and Major Kimberly Grimes, Dover Air Force Base, Delaware
Result: Comparison of sleep need versus sleep duration of C5 aircrew.
Application: Development of scheduling techniques.

Provider: DF Dinges et al.
Recipient: Major Virgil Wooten, Langley Air Force Base, Virginia
Result: Comparison of sleep need versus sleep duration of F14 pilots.
Application: Development of scheduling techniques.

Provider: CA Czeisler, DM Edgar, DF Dinges et al.
Recipient: Air Force Command Flight Surgeons and flight crews at Brooks AFB, San Antonio, TX
Result: Advisors at the Air Force Office of Scientific Research Night Operations/Human Chronobiology Workshop.
Application: Use of fatigue countermeasures in Air Force operations and deployment.

Provider: CA Czeisler, DF Dinges et al.
Recipient: Air Force Command Flight Surgeons and flight crews at Hurlburt AFB, Pensacola, Florida
Result: Provided information on fatigue countermeasures and scheduling techniques for F117 crews.
Application: Use of fatigue countermeasures the development of new scheduling techniques for F117 crews.

Provider: DM Edgar, DF Dinges et al.
Recipient: Air Force Command Flight Surgeons and flight crews at Charleston AFB, Charleston, SC
Result: Provided information on fatigue countermeasures and scheduling techniques for C-17 crews.
Application: Use of fatigue countermeasures in the development of new scheduling techniques for C-17 crews.

Provider: DF Dinges, CA Czeisler et al.
Recipient: RC Graeber, Boeing Commercial Airplane Group, Seattle, Washington
Result: Demonstration of new automated glass cockpits; presentation on PRET Center activity; advisory discussion of implications of PRET Center initiatives and findings in airplane design.
Application: Integration of information in cockpit design.

Provider: DF Dinges et al.
Recipient: RC Graeber, Boeing Commercial Airplane Group, Seattle, Washington
Result: Expert advice on incorporation of fatigue tracking technologies in the cockpit.
Application: Research and development of cockpits that incorporate fatigue monitoring technologies.

Provider: DF Dinges et al.
Recipient: Dr. Mark Rosekind, NASA Ames Research Center
Dr. R. Curtis Graeber, Boeing Commerical Airplane Group
Result: Results of experiments on restricted stimulation and posture on PVT performance lapses--potential for a metascore for performance capability.

Application: Comparisons to extant data on PVT performance in aviators.

Provider: CA Czeisler, DF Dinges et al.
Recipient: NASA - Johnson Space Center, Houston, Texas
Result: Neurobehavioral test batteries used in the PRET Center program have been flown successfully aboard STS-90 (Neurolab) and STS-95 space shuttle missions.
Application: Evaluation of astronaut performance capability.

Provider: CA Czeisler , DF Dinges et al.
Recipient: NSBRI (National Space Biomedical Research Institute)
Result: Three funded NSBRI projects interact with the PRET program, concerning the development of the biomathematical model for neurobehavioral function and assessment of circadian phase as well as the development of EEG/EOG based systems for the monitoring of vigilance and neurobehavioral performance capability.
Application: Development of biomedical countermeasures for manned space flight.

Provider: DF Dinges et al.
Recipient: NASA-Ames Research Center, Moffett Field, CA
Result: Countermeasures to performance impairment from fatigue: Study design and assessment.
Application: Design of a Boeing 747-400 simulator study on pilots evaluating alertness of pilots during a night flight after prolonged wakefulness.

Provider: DF Dinges et al.
Recipient: NASA-Johnson Space Center ,Houston, TX
Result: Selection of scientific and technical hardware for life science research on the International Space Station.
Application: Development of critically needed data on biomedical function in space flight.

Provider: DF Dinges et al.
Recipient: NASA Ames Research Center, Moffett Field, CA
Result: Consultation on development of a Boeing 747-400 simulator study evaluating alertness of pilots during a night flight after prolonged wakefulness.
Application: Development and completion of a Boeing 747-400 simulator study on pilots evaluating alertness of pilots during a night flight after prolonged wakefulness.

Provider: DF Dinges et al.
Recipient: NASA Ames Research Center , Moffett Field, CA
Result: Consultation on statistical analyses to be performed on "Alertness During a Night Flight After Prolonged Wakefulness: A Simulator Study."
Application: Data analyses completed and results presented at Aerospace Medical Association Meeting.

Provider: DF Dinges et al.
Recipient: Col. Gregory Belenky, Walter Reed Army Institute of Research
Result: Psychomotor vigilance task (PVT) hardware and software.
Application: Assessment of neurobehavioral function during cumulative partial sleep deprivation.

Provider: DM Edgar et al.
Recipient: Army Research Office
Result: Collaboration in support of studies investigating neurotrophin regulation during sleep

deprivation.

Application: Studies required use of the SCORE Sleep-Wake Bioassay Facility (Dr. Edgar's laboratory) and the expert research of Dr. Edgar and his technical staff.

Provider: DM Edgar et al.
Recipient: Cephalon, Inc., R.W. Johnson Pharmaceutical Research Institute, Gliatech Inc., Glaxo S.p.A., Co-Censys
Result: "Somnolytic index" and "locomotor activity intensity index" within the framework of the SCORE Sleep-Wake Bioassay.
Application: Pre-clinical drug screening indicator for process, application and safety decisions for advancing compounds to clinical trials.

Provider: CA Czeisler et al.
Recipient: Dr. T. Baker, Shiftwork Systems
Result: Biomathematical model of regulation of human alertness.
Application: Use of concepts derived from modeling effort to simulate shiftwork.

Provider: DF Dinges et al.
Recipient: North Atlantic Treaty Organization (NATO)
Result: Summary review of effects of melatonin on human sleep and performance.
Application: Evaluation of current potential of melatonin as a hypnotic and chronobiotic.

Provider: DM Edgar et al.
Recipient: Dr. Jeffrey Vaught and Dr. Patricia Contreras, Cephalon Inc.
Result: Pre-clinical assessment of modafinil in sleep-deprived rats.
Application: Wake promoting therapeutic for disorders of excessive sleepiness.

Provider: CA Czeisler et al.
Recipient: ALZA
Result: ALZA has reconfirmed their commitment to a cost sharing arrangement, which will be applied to the assessment of caffeine levels in plasma.
Application: Development of an electrochemistry patch for use of caffeine as a wake-promoting countermeasure in sustained operations.

Provider: CA Czeisler, DF Dinges et al.
Recipient: E Yates, Alza Corporation
Result: Consultation to standardize neurobehavioral and physiological protocols at University of Pennsylvania and the Brigham and Women's Hospital. Advisory discussion with Alza representative on use of caffeine.
Application: Development of an electrochemistry patch for use of caffeine as a wake-promoting countermeasure in sustained operations.

Provider: CA Czeisler, DF Dinges et al.
Recipient: TL Baker, Shiftwork Systems; S Koretz, E Yates Alza Corporation
Result: Meeting of PRET investigators and industry partners to discuss transition of PRET products and developmental issues.
Application: Development of an interactive computer program that provides a mathematical algorithm for scheduling countermeasure deployments.

Provider: DF Dinges et al.
Recipient: A Gevins, SAM Technology, Inc.
Result: Advisory discussion of how to utilize state-of-the-art EEG technologies for fatigue detection.
Application: Development of an EEG based fatigue detection technology.

Provider: DM Edgar, DF Dinges et al.
Recipient: Dr. Mary Carskadon and Dr. Barbara Tate
Result: Advisor to Dr. Mary Carskadon and Dr. Barbara Tate, Sleep studies in the *Octadon degus*.
Application: Studies of behavioral arousal in diurnal rodent model.

Provider: DM Edgar
Recipient: University of Alaska, Fairbanks, Alaska
Result: Collaboration in ongoing study of sleep-wakefulness in Alaskan Black Bears
Animals obtained from Air Force military staging areas in northern Alaska.
Application: Studies of how a mammalian model copes with extreme environments.

Provider: DM Edgar et al.
Recipient: Cephalon, Inc.; CoCensys, Inc.; Glaxo SpA; Gliatech, Inc.; Neurogen, Inc.; Smith-Kline Beecham Pharmaceuticals, UK.
Result: Consultation and collaboration towards pre-clinical drug discovery of novel sleep-wake therapeutics and circadian rhythm phase-shifting medications.
Application: Discovery of new wake promoting therapeutics for maintaining alertness.

Provider: DF Dinges et al.
Recipient: Lynne Brooks, Cephalon
Result: Expert advice on performance impairment from sleepiness.
Application: Novel ways to use modafinil (wake-promoting therapeutic) in promoting human alertness in operational settings.

Provider: DF Dinges et al.
Recipient: Wyeth-Ayerst
Result: Expert advice on performance impairment from dyssomnia and on sleep facilitation.
Application: Novel way to use rapidly acting sleep aids in promoting sleep in operational settings.

Provider: CA Czeisler, DF Dinges, DM Edgar et al.
Recipient: Air Force Office of Scientific Research (AFOSR), NASA and National Space Biomedical Research Institute (NSBRI) et al.
Result: Workshop on Biomathematical Models of Circadian Rhythmicity, Sleep Regulation, and Neurobehavioral Function in Humans.
Application: Use of biomathematical models for optimizing human functioning.

Provider: DM Edgar
Recipient: Hypnion, Inc., Worcester, MA
Result: Creation of new sleep Biotechnology Company founded upon the SCORE sleep-wake bioassay technology and SCORE Sleep-Wake Pharmacological Database.
Application: Commercial screening of drugs for sleep-wake effects and/or side effects. Hypnion also has in-licensing efforts to identify novel safe & effective soporific drugs and wake promoting therapeutics for maintaining alertness.

Provider:	DM Edgar
Recipient:	Hypnion, Inc., Worcester, MA
Result:	Transfer of SCORE-2000 Sleep-Wake Bioassay Technology to Hypnion Inc., under an exclusive corporate licensing agreement with Stanford University.
Application:	Commercial screening of drugs for sleep-wake effects and/or side effects. Hypnion also has in-licensing efforts to identify novel safe & effective soporific drugs and wake promoting therapeutics for maintaining alertness.

Provider:	DF Dinges
Recipient:	Col. Peter Demitry, Chief, Human Systems Integration, Division, Directorate of Requirements, Langley Air Force Base
Result:	Activities and results of Center research to be transitioned to Human Systems Integration, Division, Directorate of Requirements, Langley Air Force Base
Application:	Use of Ceter research in management of AF personnel alertness and performance.

9. NEW DISCOVERIES, INVENTIONS, PATENTS

SCORE-2000: AFOSR PRET funding, and equipment funding provided under DURIP, made possible the creation of a new-generation SCORE Sleep-Wake Bioassay system called SCORE-2000. This technology constitutes the most advanced pre-clinical sleep-wake bioassay system of its kind. SCORE-2000 technological advancements include expanded artificial intelligence, compatibility with multi-algorithmic consensus scoring, expanded variable acquisition, double the animal capacity, and intrinsic Internet interface. The latter feature allows SCORE-2000 systems to serve as remote sleep-scoring nodes that can be fully monitored and controlled in real time from anywhere in the world via secure tunneling protocols in a Windows-2000 OS environment. A new security provision also allows control over user permissions. Completion of this work satisfies the proposed expanded PRET research & development objectives and goals of the DURIP. SCORE-2000 was obtained under a procurement agreement between Stanford Software Systems and Stanford University. The copyright to SCORE-2000 is owned by Dr. Dale M. Edgar (Center Co-P.I.), with exclusive sub-license authority granted to Stanford University. SCORE-2000 and the SCORE Sleep-Wake Pharmacology Database have been licensed to Hypnion, Inc. (Worcester, MA) for commercial drug discovery and development work. Dr. Edgar is a co-founder of Hypnion, Inc.

10. HONORS/AWARDS.

David F. Dinges, Ph.D.	Fellow, Academy of Behavioral Medicine Research (1995)
David F. Dinges, Ph.D.	Excellence in Teaching Award, University of Pennsylvania (1996)
Dale M. Edgar, Ph.D.	Promotion to Associate Professor, Department of Psychiatry & Behavioral Sciences, Stanford University (1996)
David F. Dinges, Ph.D.	Honorary Medal, Swedish Physicians Society (1997)
Charles A. Czeisler, Ph.D., M.D.	Keynote Address, Association of Professional Sleep Societies (1998)
David F. Dinges, Ph.D.	Dean's Award for Excellence in Basic Science Teaching, University of Pennsylvania School of Medicine (1999)
David F. Dinges, Ph.D.	Professor of the Year, Biological Basis of Behavior Society, University of Pennsylvania School of Medicine (2000)
David F. Dinges, Ph.D.	NASA TIGR Aviation Safety Award to the Fatigue Countermeasures Project Team for "Turning Goals into Reality" (2000)
David F. Dinges, Ph.D.	President-Elect, Sleep Research Society (2000)

11. CENTER SCIENTIFIC ADVISORY BOARD

Civilian members

Professor Torbjorn Åkerstedt, Ph.D., Karolinska Institute, Stockholm, Sweden
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